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Review article

Early progression of cardiac allograft vasculopathy assessed by quantitative coronary angiography: A single centre prospective study

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ABSTRACT

Introduction: Early diagnosis of cardiac allograft vasculopathy (CAV) becomes a crucial step in management of post-transplant patients since it can be attenuated by specific clinical approaches.

Materials and methods: We enrolled 48 consecutive patients in this prospective, observational, single centre study. Early development of CAV was assessed by two independent reviewers using quantitative coronary angiography (QCA) in the 1st and 12th month after heart transplantation (HTx). We examined the relationship between CAV and selected clinical and serological variables.

Results: A significant mean lumen diameter (MLD) loss was observed in all major coronary artery branches within 12 months after HTx. MLD loss was as follows – RCA (3.52 mm → 3.25 mm, $P = 0.0008$), LCx (3.68 mm → 3.42 mm, $P < 0.0001$) and LAD (3.95 mm → 3.69, $P < 0.0001$). Among the patient cohort, 14 CAV rapid progressors (14/48, 29.2%) were identified. Their sum of MLD loss in all monitored arteries within 12 months after HTx reached ≥10%. An increased heart rate in the 12th month after HTx reflected the younger age of a donor ($P = 0.01$), but was not associated with rapid progression of CAV. The most important predictor of rapid progression of CAV was increased serum level of B-type natriuretic peptide (BNP) soon after HTx (3rd day after HTx, $P = 0.04$).

Conclusion: A significant reduction of MLD was observed in all major coronary arteries as early as within the first year after HTx. Early elevation of BNP serum levels predicted rapid progression of CAV. The presumption that faster heart rate is involved in the development of CAV in HTx recipients was not confirmed.

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Introduction

Cardiac allograft vasculopathy (CAV) is the leading cause of late morbidity and mortality in heart transplant (HTx) patients and limits long-term survival [1,2]. Various studies attempted to evaluate predictors of CAV.

Since some experimental and clinical data suggest that sustained elevation of heart rate may contribute to the pathogenesis of vascular disease [3,4], sinus tachycardia in HTx patients resulting from cardiac denervation [5] could be one of the contributing factors in development of CAV. However, contradictory data exist on this relationship in the HTx population [6,7].

Another unanswered question in management of post-transplant patients is whether the development of CAV could be attenuated. Recent studies show that early conversion to mTOR inhibitor (sirolimus, everolimus) may slow down the plaque progression compared with continued calcineurin inhibitor (CNIs) therapy [8,9]. On the other hand, late conversion to this drug regimen may be associated with increase in plaque necrotic core and dense calcium volume [10]. Therefore, early detection of CAV ''rapid progressors'' might be important in the management of CAV.

The main aim of our study was to evaluate the prognostic implication of increased heart rate and selected serum biomarker levels during the post-transplant period in relation to early CAV development.

Patients and methods

This was a prospective, observational, single centre study. The patient population consisted of 48 consecutive subjects who underwent orthotopic heart transplantation (93 patients transplanted between 2012–2013) at the Institute for Clinical and Experimental Medicine (IKEM) in Prague. This centre is larger of the two transplant centres in the Czech Republic. The study complies with the Declaration of Helsinki, the study protocol was approved by the local ethics committee and all participating patients signed the informed consent.

Patients who were unwilling to sign the informed consent form were not included in the study.

All relevant data were recorded in a standardized form that included donor and recipient baseline characteristics, aetiology of heart failure, smoking habit, the presence of arterial hypertension or diabetes mellitus, details about immunosuppressive medication, acute rejection and cytomegalovirus infection. Serological levels of hsTnT, BNP and galectin-3 were measured at selected periods (3, 7, 30 days and 3, 6 and 12 months after HTx).

Patients were managed according to the clinical protocol of our HTx programme. The immunosuppression regimen included tacrolimus, mycophenolate mofetil (MMF) and steroids. Anti-thymocyte globulin (ATG-Fresenius S.) at 1.25 mg/kg i.v. was used as induction therapy for all patients in the first two days after HTx and later selectively according to lymphocyte count. Valganciclovir (VGC) as a general prophylaxis was administered in a dose of 900 mg per day and trimethoprim–sulfamethoxazole (TMP–SMX) in a dose of 480 mg per day (TMP 80 mg/SMX 400 mg). The duration of the treatment was 100 and 90 days, respectively. The beta-blocker use and its daily dose were also assessed in all patients. Ivabradine or other heart rate-modifying medications were not used in the study cohort.

The acute cellular and/or humoral rejections were evaluated analyzing regular diagnostic endomyocardial biopsies (EMB). Endomyocardial biopsies were planned and performed according to the institutional protocol. Patients underwent biopsy every week until 30 days post-transplant, and then every 2 weeks for 3 months, followed by once a month for 6 months. The last regular biopsies were scheduled on the 9th and 12th month after the heart transplant. In total, 10 EMB were performed in each patient during the first year after heart transplant.

The presence and extent of CAV were assessed during in-hospital stay in the 1st and 12th month after HTx, using coronary angiography (Siemens Axiom DFC/DTC). To improve a contrast image quality and minimize the amount of applicable contrast dose we used the contrast injection system – ACIST CVi. To standardize CAV assessment, quantitative coronary angiography (QCA) was employed (ACOM.PC 5.01; QUANTCOR.QCA, ver. 5.0 – catheter calibration, user defined

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