Original paper

Microcirculation and intravascular imaging assessment in heart transplant recipients for detection of cardiac allograft vasculopathy: a pilot study

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Abstract

Introduction: Cardiac allograft vasculopathy (CAV) is the leading cause of late mortality after heart transplantation (HTx). It is a progressive and diffuse process involving both the epicardial coronary arteries and the microcirculation, caused by immunologic and non-immunologic factors resulting in localized inflammation. Microcirculatory and intravascular imaging assessments help characterize the physiological phenotype of patients and better predict their prognosis.

Aim: To conduct a comprehensive imaging and functional evaluation of the coronary arteries for early detection of vasculopathy in patients after heart transplantation.

Material and methods: This is a prospective, single-center study enrolling patients who underwent heart transplantation and their first coronary angiography (CA) within the first 2 years after HTx. In all patients, intravascular ultrasound was performed to detect thickening of the intima-media complex. Additionally, functional assessment of coronary arteries and microcirculation was done.

Results: Vessels from 10 patients (mean age: 56.6 ±11.6 years) within the first 2 years after transplantation were assessed with additional left anterior descending (LAD) evaluation. A plaque burden of > 30% in the segment of the most significant stenosis in the LAD was observed in 70% of vessels, and thickening of the intima-media complex > 0.5 mm was observed in 60% of cases. Fractional flow reserve (FFR) < 0.8 occurred in 1 patient. The mean index of microcirculatory resistance (IMR) was 17 ±10, and mean coronary flow reserve (CFR) was 4.33 ±1.1.

Conclusions: In heart transplantation patients, comprehensive angiographic, imaging, and physiological evaluation including microcirculation assessment may allow for early detection of allograft vasculopathy.

Key words: heart transplantation, cardiac allograft vasculopathy, functional assessment, microcirculation.

Summary

This is a pilot study on a unique group of patients after heart transplantation in which we make a comprehensive angiographic, imaging evaluation and physiology assessment with microcirculation for early detection of allograft vasculopathy and to assess the impact of early detection of cardiac allograft vasculopathy on the long-term prognosis.

Introduction

Cardiac allograft vasculopathy (CAV) is the leading cause of late mortality after heart transplantation (HTx) and is the most frequent form of chronic rejection [1]. CAV is a progressive and diffuse process involving both the epicardial coronary arteries and the microcirculation, caused by immunologic and non-immunologic factors resulting in localized inflammation. Approximately 10% of patients have angiographic coronary artery disease at 1 year, 50% at 5 years, and 80% at 15 years, with long-term mortality increasing with angiographic severity. It

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is recommended to perform annual coronary angiography to assess the development of CAV; however, coronary angiography has limited value for predicting the progression of vasculopathy and subsequent events in cases of no or mild angiographic CAV [2–6]. The recent International Society for Heart and Lung Transplantation (ISHLT) guidelines for heart transplant recipients provided Class IIa recommendations for the use of intracoronary imaging by intravascular ultrasound (IVUS) to detect vasculopathy and to provide prognostic information [7]. Assessing coronary physiology using a pressure guidewire has been well validated in the general population; nowadays, we also have the ability to invasively assess the microcirculation. The comprehensive physiological assessment of the epicardial coronary arteries and microcirculation has helped characterize the physiological phenotype of patients and better predict their prognosis. Similarly, in transplant patients, fractional flow reserve (FFR) correlates with plaque volume assessed by IVUS, and the index of microcirculatory resistance (IMR) measured after transplantation has been shown to predict the development of CAV, poor graft function, and long-term mortality [8].

Aim

The aim of our study is to conduct a comprehensive imaging and functional evaluation of the coronary arteries, including early detection of vasculopathy in patients undergoing heart transplantation.

Material and methods

Study design and patients

This is a single-center, prospective study. Consecutive patients aged over 18 years who were referred for routine coronary angiography after orthotopic heart transplantation (OHT), performed according to local protocol at 16 months post-transplant, at a high-volume tertiary referral hospital in southern Poland (the Silesian Center for Heart Disease in Zabrze), were included. During each coronary angiography, we used IVUS to obtain morphological plaque measurements in the left main (LM) and left anterior descending (LAD) coronary arteries. We also performed a functional assessment of the LAD, including FFR, IMR and coronary flow reserve (CFR).

Coronary angiography, intravascular, and physiological assessment

Post-transplantation baseline coronary angiography was performed using standard techniques. The angiographic severity of CAV after transplantation was evaluated according to the ISHLT classification:

- CAV0: Lack of angiographically detectable lesions.
- CAV1: Mild disease with diameter stenosis of < 50% in the left main coronary artery or < 70% in other segments.
- CAV2: Moderate disease with one or more lesions showing diameter stenosis of ≥ 70% in a major vessel or ≥ 70% stenosis in branches of two vascular systems.
- CAV3: Severe disease involving the left main coronary artery with ≥ 50% stenosis, two or more major vessels with ≥ 70% stenosis, ≥ 70% stenosis in branches of all three systems, or CAV1–2 with allograft dysfunction.

After performing coronary angiography, FFR, IMR, and CFR were measured using a pressure-temperature sensor-tipped guidewire (Abbott Vascular) placed in the distal part of the LAD. FFR was defined as the mean distal coronary pressure divided by the mean aortic pressure at maximal hyperemia. The IMR was calculated as the distal coronary pressure at maximal hyperemia divided by the inverse of hyperemic mean transit time. CFR was calculated as resting mean transit time divided by hyperemic mean transit time. Resting and hyperemic mean transit times were measured using standard thermodilution techniques. Maximal hyperemia was induced with the administration of intracoronary adenosine.

IVUS was performed in the LAD and LM using a 60 MHz IVUS catheter (ACIST Kodama HD IVUS, Boston Opticross HD IVUS) with automatic pullback. Maximal intimal thickness (MIT) was measured in the middle part of the LM artery, at the ostium of the LAD, and in segments 6 and 7.

Results

Baseline characteristics

The clinical characteristics of the study population are summarized in Table I.

Ninety percent (n = 9) of patients were male, the mean age was 56.6 ±11.6 years, and the median time between transplantation and coronary angiography was 16 months. According to the ISHLT CAV classification, 7 patients had CAV0 and 3 patients had CAV grade ≥ 1 (CAV1: 3 patients; CAV2: 0 patients; CAV3: 0 patients). Three patients had grade 2B or 3 acute cellular rejection by the time of the first coronary angiography.

Coronary physiology and intravascular assessment

An FFR < 0.8 was observed in 1 patient, with a mean FFR of 0.93 ±0.05. Two patients had elevated microvascular resistance (IMR > 24); the mean IMR for the entire population was 17 ±10, and the mean CFR was 4.33 ±1.1. A plaque burden of > 30% in the segment with the most significant stenosis in the LAD was observed in 70% of the vessels, and thickening of the intima-media complex (MIT) > 0.5 mm was observed in 60% of cases (Table II).

Discussion

This pilot study provides a comprehensive evaluation of physiological and intravascular assessments in

Table I. Baseline characteristics and treatment at discharge

Variable	Overall (*N* = 10)
Age [years]	56.6 ±11.5
Male sex	9 (90%)
Diabetes	5 (50%)
Hypertension	4 (40%)
Hypercholesterolemia	6 (60%)
Total cholesterol [mmol/l]	3.63 ±1.1
LDL-C [mmol/l]	1.71 ±1.1
Creatinine [µmol/l])	107.3 ±35.1
Ejection fraction (%)	56.7 ±2.4
Donor/recipient sex mismatch	5 (50%)
Donor age [years]	44.9 ±7
Ischemic time [min]	219 ±79
Cellular rejection > 2	3 (30%)
Tacrolimus	10 (100%)
Mycophenolate	6 (60%)
Sirolimus/everolimus	4 (40%)
Statin	10 (100%)

LDL-C – low-density lipoprotein cholesterol.

Table II. Angiographic, physiological, and imaging characteristics of patients

Variable	Overall (*N* = 10)
ISHLT CAV0	7 (70%)
ISHLT CAV1	3 (30%)
ISHLT CAV2	0
ISHLT CAV3	0
FFR	0.93 ±0.05
IMR	17 ±10.06
CFR	4.33 ±1.09
MIT > 0.5 mm	6 (60%)
Plaque burden > 30%	7 (70%)
Plaque burden LM (%)	17.5 ±7.7
Plaque burden ostium LAD (%)	22.4 ±8.5
Plaque burden 10 mm LAD (%)	25.1 ±9.4
Plaque burden 25 mm LAD (%)	32.3 ±12.3

LAD – left anterior descending artery, CAV – cardiac allograft vasculopathy, ISHLT – International Society for Heart and Lung Transplantation, FFR – fractional flow reserve, IMR – index of microcirculatory resistance, CFR – coronary flow reserve, MIT – maximal intimal thickness, LM – left main coronary artery.

patients undergoing routine coronary angiography after OHT. Although the diagnosis of CAV and the prognostication of subsequent events in routine clinical practice are still based on anatomical assessment through coronary angiography, recent data highlight the role of intracoronary imaging (IVUS, OCT) and invasive wire-based physiological evaluation of epicardial arteries and microcirculation [8].

A pivotal study on invasive coronary physiological assessment in OHT recipients showed that FFR was associated with the risk of death and retransplantation at 10 years [8]. While coronary angiography is the gold standard for CAV diagnosis and classification, it may fail to detect CAV. Nagumo *et al.* found that one-third of patients with ISHLT CAV0 had functionally significant CAV (i.e., FFR ≤ 0.80) [9]. Ahn *et al.* demonstrated that microvascular dysfunction (IMR ≥ 25 or CFR ≤ 2.0) 1 year after heart transplantation is common and serves as a significant predictor of death or retransplantation at 10 years [10]. Kim *et al.* described the relationship between thickening of the MIT complex and adverse events in long-term follow-up [11].

Considering the available data, we designed our study to combine angiographic assessment with a comprehensive functional evaluation of the coronary vessels and imaging of the LAD. As demonstrated by Floré ***et al.***, the LAD has the highest diagnostic accuracy of all vessels in detecting a patient's highest overall Stanford grade and is sufficient to detect early CAV [4].

Detection of vasculopathy plays a critical role in guiding immunosuppressive therapy. It can lead to a switch from a maintenance regimen to more aggressive immunosuppression or to adding drugs that target specific pathways involved in vasculopathy [12]. The presence of vasculopathy necessitates more frequent monitoring of the patient's graft function and vascular status. This ongoing surveillance can help in timely adjustments to immunosuppressive therapy based on changes in the patient's condition. In cases where vasculopathy is significant, adjustments may not only be pharmacological; lifestyle modifications, such as managing cardiovascular risk factors (e.g., hypertension, dyslipidemia), may also be emphasized alongside adjusting immunosuppressive therapy.

In conclusion, detecting vasculopathy serves as a crucial factor in the evaluation and management of patients after OHT. This detection not only influences immediate treatment decisions but also shapes long-term strategies for optimizing patient care and improving outcomes. Only a comprehensive assessment in heart transplant recipients using the latest diagnostic techniques allows for a full evaluation of the progression of vasculopathy. However, due to the rarity of heart transplantation and the small population of patients, further studies on this issue are necessary.

Conclusions

In heart transplant patients, comprehensive angiographic, imaging, and physiological evaluation including microcirculation assessment allows for early detection of allograft vasculopathy. In future, it may help to distinguish a group of patients requiring more frequent follow-up and more aggressive medical therapy.

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Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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