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International Journal of Cardiology 103 (2005) 201–206

International Journal of Cardiology

www.elsevier.com/locate/ijcard

Coronary flow reserve impairment predicts cardiac events in heart transplant patients with preserved left ventricular function

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Received 25 May 2004; received in revised form 25 October 2004; accepted 18 December 2004

Abstract

Background: The impact of allograft vasculopathy on the coronary circulation and consequently on cardiac outcome may be expressed by coronary flow reserve (CFR) impairment. Therefore, we aimed to evaluate CFR and its relation to cardiac events in heart transplant patients.
Methods: Twenty-three patients, 2 female, with left ventricular ejection fraction >45% were studied 76±30 months after heart transplantation. They were divided into 2 groups according to coronary angiography: Group A, 10 patients with significant coronary artery disease (stenosis≥50%) and group B, 13 patients without significant stenosis. Twenty healthy subjects, 13 female, served as controls. Coronary flow velocity reserve (CFVR) was assessed by transesophageal echocardiography and calculated as the ratio of maximal (i.v. adenosine, 140 μg/kg/min) to baseline coronary velocities. Patients were followed for a mean of 25 months for cardiac events.
Results: Compared to controls, heart transplant groups showed significantly higher baseline coronary flow velocities (51±27, 38±12 and 32±12 cm/s, respectively) and lower maximal coronary velocities (90±52, 112±33 and 118±24 cm/s), resulting in a reduced CFVR (1.9±1.0, 3.0±0.5 and 3.8±1.2). Multivariate analysis identified heart transplantation and epicardial coronary artery disease as the only variables independently related to CFVR. Hypertension was positively related to baseline while diabetes inversely related to maximal coronary flow velocities. A CFVR <2.3 was a marker for cardiac events (4 deaths, 1 heart failure).
Conclusion: CFVR impairment, particularly in the presence of epicardial coronary artery disease, follows heart transplantation and is associated with a worse outcome.

Keywords: Heart transplantation; Coronary artery disease; Transesophageal echocardiography

1. Introduction

Allograft coronary artery disease is recognized as the main clinical complication affecting long-term survival in heart transplant patients [1]. Both epicardial coronary vessels and the microvasculature seem to be affected by what is thought to be an immune-mediated damage [2]. The identification of this disorder is a medical challenge, since angina may be absent due to heart denervation [3], and noninvasive tests may be misleading [4]. Therefore, the diagnosis must rely upon coronary angiography, which may substantially underestimate the frequency and severity of the disease [5]. Additionally, coronary angiography cannot functionally assess microvasculature and major vessels.

Coronary flow reserve (CFR) measurements may estimate the physiologic impact of allograft disease on the coronary circulation. Results ranging from impaired to high-normal CFR have been reported in this setting [6–8]. In addition to allograft vasculopathy, several other mechanisms such as hypercholesterolemia, hypertension, diabetes mellitus and left ventricular hypertrophy [9–11], highly prevalent in this population, may account for CFR impairment. Investigation, however, is limited by the need to perform invasive, expensive, or time-consuming procedures. Transesophageal echocardiography has been shown to be a

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doi:10.1016/j.ijcard.2004.12.017

feasible means of estimating coronary flow velocity reserve (CFVR) by measurements of blood flow velocities in the left anterior descendant coronary artery [12]. Alternatively, it has been used to assess patients with coronary artery disease [13,14]. It might represent an alternative for non-invasively assessing CFR in heart transplant patients.

Accordingly, this study aimed 1) to investigate the relevance of CFVR in heart transplant recipients by means of transesophageal echocardiography, 2) to identify clinical determinants involved in CFVR impairment, and 3) to prospectively examine its value in predicting long-term outcome.

2. Materials and methods

We studied 31 asymptomatic patients, >18 years old, 2 female (premenopausal), under a triple-drug immunosuppressive regimen consisting of cyclosporine, prednisone, and azathioprine. Patients were on continuous antihypertensive therapy (calcium-channel blockers and angiotensin-converting enzyme inhibitors). None of the patients was under beta-blockers. Only one heart transplant patient was a smoker.

Inability to obtain adequate coronary Doppler tracings, echocardiographic left ventricular ejection fraction <45% [15], histological features of allograft rejection on endomyocardial biopsy [16], significant valvular heart disease and history of asthma were exclusion criteria.

Due to the major effect of epicardial coronary artery disease on CFVR, two groups of patients, A and B, were constituted according to the angiographic presence or absence of ≥50% coronary artery stenosis, respectively (Table 1). The influence of heart transplantation on CFVR was tested by comparison of CFVR measurements with a control group consisting of 20 voluntary healthy subjects (13 female, aged 49.1±10.7 years), with normal physical and laboratory examinations and a negative treadmill test. None of the subjects had a family history of coronary artery disease and all of them were nonsmokers. Six women were postmenopausal, however none was under hormone replacement therapy.

After the end of the initial investigation, heart transplant patients were followed for 25±10 months to assess event-free outcome. The following cardiac events were established as primary end-points: cardiac death, acute myocardial infarction and new onset of heart failure

Table 1
Patient demographics

	Group A (n=10)	Group B (n=13)	Control (n=20)
Age (years)	53±10	43±13	49±11
Sex (M/F)	9/1(*)	12/1(*)	13/7
BMI (kg/m^2)	28±5	24±5	25±3
Cholesterol (g/dl)	231±72	177±41(*)	194±28
Hypertension (n)	9	10	NA
Diabetes (n)	4	1	NA

n=number of patients; M=male; F=female; BMI=body mass index; (*)=p<0.05; NA=non-applicable.

The study was approved by the Institutional Ethical Committee for Clinical Research. All subjects signed an informed consent form to participate.

2.1. Echocardiography

Two-dimensionally guided M-mode echocardiography was undertaken (Phillips-ATL HDI 5000 or 3000 system with a 2–4 MHz transducer) according to the American Society of Echocardiography guidelines [17]. Left ventricular ejection fraction was calculated according to the Teichholz correction of cube measurements [18]. Left ventricular mass was calculated using the cube formula corrected for the Penn convention, where left ventricular mass=0.8×(ASE cube left ventricular mass)+0.6 [19]. Due to inevitable discrepancies between the donor heart and the recipient's body size, LV mass was not indexed to body surface area or height. Values of left ventricular mass higher than 219 g for men and 164 g for women were considered left ventricular hypertrophy [20].

2.2. Transesophageal echocardiography

Patients were requested to fast for 6 h and to abstain from caffeine-containing products for at least 12 h before the examination. After topical oropharyngeal anesthesia with lydocaine and light sedation with midazolam, the probe was gently introduced through the mouth down to the proximal esophagus until the aortic valve was visualized. A multiplane transducer (4–7 MHz, HDI, Phillips, Bothel, CA) was used to perform the examination. With the echocardiographic plane at approximately 0°, small adjustments were made to visualize the left main coronary artery and its bifurcation in left anterior descending and circumflex coronary artery. With the help of color flow mapping, the sample volume was placed in the proximal segment of the left anterior descending coronary artery. After obtaining baseline flow velocities, 140 μg/kg/min adenosine was continually infused in a peripheral vein during 6 min. Heart rate, blood pressure and electrocardiogram were monitored throughout the examination. Images were recorded on videotape for posterior off-line measurements. The ratio of maximal diastolic peak flow velocity to baseline diastolic peak flow velocity was used as an index of CFVR. The average of three consecutive Doppler measurements was considered for analysis. Coronary flow velocities from Doppler recordings of 10 patients were re-measured after 2 months in order to assess intra and interobserver variability.

2.3. Coronary angiography

Coronary angiography was undertaken during the same week of the transesophageal echocardiography by