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Persistent mild lesions in coronary angiography predict poor long-term survival of heart transplant recipients

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BACKGROUND: Even though coronary angiography (CAG) underestimates coronary allograft vasculopathy (CAV) development, especially in the distal parts of arteries, it remains a frame of reference for International Society for Heart and Lung Transplantation (ISHLT) CAV classification. A retrospective analysis was performed to assess the prognostic value of CAG findings.

METHODS: Among 310 orthotopic heart transplantation (OHT) recipients with at least 2 CAGs at 2-year intervals, we identified 197 (146 men and 41 women; 55 ± 13 years) without lesions (Group 0), 27 (15 men and 12 women; 58 ± 8 years) in whom mild changes remained in consecutive CAGs (Group 1), 28 (24 men and 4 women; 58 ± 10 years) in whom mild lesions decreased in consecutive CAGs (Group 1REG), and 58 (53 men and 5 women; 56 ± 10 years) in whom the stenosis criteria of ISHLT CAV 2 or 3 were covered (Group 2). We compared survival and other clinical variables among the groups.

RESULTS: The average follow-up was 10 ± 4 years. Forty-one (21%) deaths occurred in Group 0, 15 (56%) in Group 1 ($p = 0.002$), 9(31%) in Group 1REG (p = NS), and 26 (46%) in Group 2 ($p = 0.004$, chi-square test). Time free from all-cause death was significantly shorter in Group 1 (T1/2 = 8 years) than in Group 0 (T1/2 = 15.5 years; $p = 0.00072$, log-rank test). Time free from cardiovascular death was significantly shorter in Groups 1 and 2, as was time free from CAV-related death in Groups 1, 1REG, and 2. Multivariate analysis, using a Cox proportional hazards model, revealed that Group 1 inclusion criterion of CAG findings is an independent predictor of all-cause death, cardiovascular death, and CAV-related death.

CONCLUSIONS: Persistent mild coronary lesions, observed in consecutive CAG, predicted shorter survival of OHT recipients.

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Despite many debates dealing with the immunologic and non-immunologic origin of coronary allograft vasculopathy (CAV), as well as the optimal diagnostic approach to describe its natural history, coronary angiography (CAG) remains a widely accepted standard that was validated by

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the recent statement from International Society for Heart and Lung Transplantation.[1] Although the early experience with intravascular ultrasound imaging suggested that coronary artery intimal thickening was essential for CAV prognostication, further common observations established the leading role of the preserved artery lumen (assessable with CAG) in keeping myocardium viable.[2] This change has occurred despite universal agreement that the pathology of CAV is not limited to narrowing of the epicardial arteries, with a special concern about the distal intermyocardial arteries. These low-diameter vessels have remained outside the area of possible coronary intervention treatments, and the usefulness of the only available diagnostic tool to describe CAV, which is an endomyocardial biopsy specimen, has been controversial.[3,4]

Therefore, the only logical option seems to be to obtain as much valuable clinical information as possible from repeated CAGs. The main aim in performing CAG is to look for significant stenosis in the epicardial vessels. CAG is also performed to search for some features that are typical of poor coronary outflow, with markedly slowed contrast passage being the most characteristic for CAV, thus constituting a diagnosis, even in the absence of any focal narrowing.[5] However, hemodynamically non-significant lesions in the epicardial arteries are rarely a matter of concern.

It is worth underlining that heart transplant recipients are a very rare population in whom elective CAGs are performed every 12 to 24 months, even in the absence of any clinical symptoms or signs of coronary artery disease. This allows us to observe the beginning and dynamics of the disease. To our surprise, these dynamics are not always progressive—in some individuals, non-significant lesions seem to disappear, whereas in others, they remain stable. We performed a retrospective analysis of the long-term results from all of our patients undergoing routine CAG evaluations to assess the prognostic value of these phenomena.

Methods

A retrospective cross-sectional analysis was performed of the 310 patients who underwent orthotopic heart transplantation (OHT) at the Silesian Center for Heart Disease from 1987 to 2010, in whom at least 2 CAGs were performed at 2-year intervals after OHT. The patients were divided into 4 groups, according to the degree of the lesions in the epicardial arteries: Group 0 (reference group): 197 patients without any lesions in any CAG; Group 1: 27 patients in whom mild changes were observed that remained in consecutive CAGs; Group 1REG: 28 patients in whom mild lesions were diagnosed in at least 1 CAG but which disappeared or substantially decreased in consecutive CAGs; and Group 2: 58 patients in whom the stenosis criteria of ISHLT CAV 2 or 3 were met in at least 1 CAG.

The demographic and clinical characteristics of the patients are presented in Tables 1 and 2. Classification of the coronary lesions was based on the current ISHLT working formulation of CAV; however, left ventricle performance was not considered.[1]

Table 1 Comparison of Qualitative Variables

	Group 0	Group 1	Group 1REG	Group 2			
	($n = 197$)	($n = 27$)	($n = 28$)	($n = 58$)	p-value (chi-square test)[a]		
Patient variables	(%)	(%)	(%)	(%)	Group 1 vs 0	Group 1REG vs 0	Group 2 vs 0
Females, %	20.8	3.7	14.3	8.6	0.0611	NS	0.0338
Ischemic etiology of heart failure	34	44.4	46.4	53.4	NS	NS	0.0014
Arterial hypertension	79.7	70.4	82.1	72.4	NS	NS	NS
Diabetes	47.7	59.3	50	44.8	NS	NS	NS
Diabetes requiring insulin	23.4	48.1	32.1	32.8	0.0121	NS	NS
BMI $>$ 25 kg/m^2	53.8	69.2	63	55.2	NS	NS	NS
BMI $>$ 30 kg/m^2	14.7	34.6	18.5	17.2	0.0239	NS	NS
CPK $>$ 200 units/ml	15.2	7.4	10.7	17.2	NS	NS	NS
Cholesterol $>$ 5.0 mmol/liter	38.6	44.4	32.1	34.5	NS	NS	NS
Triglycerides $>$ 1.65 mmol/liter	34	48.1	32.1	34.5	NS	NS	NS
HDL-C $<$ 1.0 mmol/liter	12.7	18.5	21.4	35.1	NS	NS	0.0001
LDL-C $>$ 3.0 mmol/liter	44.2	44.4	46.4	39.7	NS	NS	NS
Medications							
Cyclosporine	53.8	51.9	71.4	51.7	NS	NS	NS
Tacrolimus	26.9	29.6	17.9	17.2	NS	NS	NS
Mycophenolate mofetil	48.2	48.1	32.1	32.8	NS	NS	0.0373
Everolimus	17.8	7.4	10.7	24.1	NS	NS	NS
Sirolimus	5.1	14.8	3.6	15.5	NS	NS	0.0078
Azathioprine	5.1	7.4	7.1	10.3	NS	NS	NS
Prednisone	12.7	11.1	10.7	10.3	NS	NS	NS
Statin	68.5	74.1	60.7	65.5	NS	NS	NS

BMI, body mass index; CPK, creatine phosphokinase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NS, not significant.

[a] P-values $\geq$ 0.1 were considered not significant.