ORIGINAL ARTICLE

Influence of donor-transmitted coronary artery disease on long-term outcomes after heart transplantation - a retrospective study

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ABSTRACT

Background

Cardiac allograft vasculopathy (CAV) is an important cause of late mortality after heart transplantation, which may be influenced by preexisting coronary disease (CAD) in the donor heart.

Methods

The aim of this study was to verify whether CAD in the donor heart had any influence on survival, cardiac-related adverse events (CRAEs), and coronary disease progression after transplantation. Donor coronary angiography performed in 289 hearts showed absence of CAD in 232 (no-CAD group) and moderate (≤50%) stenoses (CAD group) in 57. The 2 groups were compared for survival, freedom from CRAEs, and development of grade ≥ 2 CAV after transplantation.

Results

Of 30-day mortality and postoperative complication rate was similar as mean follow-up (76 ± 56 and 75 ± 55 months) for no-CAD and CAD ($P = 0.8$). Ten-year actuarial survival was 58 ± 4% and 62 ± 7% for no-CAD and CAD ($P = 0.4$). Ten-year freedom from grade ≥ 2 CAV and from CRAEs was 81 ± 4% and 66 ± 5% vs 75 ± 8% and 67 ± 9% in no-CAD and CAD ($P = 0.9$ and 0.9, respectively).

Conclusions

Donor hearts with moderate CAD did not affect survival, freedom from CRAEs and did not accelerate development of high-grade CAV after transplantation supporting the use of such grafts to expand the donor pool. Routine use of coronary angiography in donor selection appears justified.

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Key words
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Introduction

Cardiac allograft vasculopathy (CAV) represents an important cause of long-term mortality and morbidity after heart transplantation (HTx) [1-3]. Although the pathology of CAV onset is not yet fully elucidated, it has been suggested that a preexisting coronary atherosclerotic disease (CAD) in the donor heart could influence the subsequent development of CAV after HTx [3-5]. In fact, it has been hypothesized that in this condition the endothelium of the donor coronary arteries might be more prone to develop a fibro-proliferative process, possibly providing a trigger for the subsequent progression of CAV. However, no clear relationship between a preexisting donor CAD and development of CAV has been so far demonstrated since few studies have focused on this specific issue [5-10]. Therefore, the present study aimed to verify whether CAD in the donor graft might have any influence on subsequent CAV progression as well as any adverse effect on long-term survival after HTx.

Methods

Pre-HTx evaluation

Donors and recipients were matched for ABO blood type and body weight, considering severe clinical status and longer time on waiting list as priority. Prior to their procurement, all donor hearts were evaluated by 2D transthoracic echocardiography and, after median sternotomy, under direct vision to exclude any wall motion abnormalities; at the same time, digital exploration of the epicardial surface was carried out to detect the presence of calcifications on the subepicardial coronary arteries. Since 1999, coronary angiography was indicated in all donors $\geq$ 40 years of age and in those with known risk factors for CAD. Donors without severe CAD, defined as presence of $\leq$ 50% stenosis of the proximal or middle third of at least one major coronary vessel, were generally accepted for HTx. Donors coming from other hospitals, where coronary angiography was not available, were either transferred elsewhere or at our center if possible, or generally refused for HTx.

Study design

All patients who underwent HTx using a graft evaluated with coronary angiography prior to the procurement were divided into two groups according to the presence of nonsevere CAD of the donor heart (Group CAD and Group no-CAD, respectively). The 2 groups were evaluated and compared, the primary endpoints being early (up to 30-days after HTx) and late survival, and the secondary endpoints incidence, development, and progression of grade $\geq$ 2 CAV (since all patients of CAD group were *per-definition* affected by CAV of grade 1) as defined by the International Society for Heart and Lung Transplantation (ISHLT) [1], and freedom from a composite of cardiac-related adverse events (CRAEs) that include cardiac-related death, hospital re-admission for cardiac failure, pacemaker implantation, coronary artery revascularization, and heart retransplantation.

Patients undergoing re-HTx (n = 5), multiple organ transplantation (n = 12), and those receiving an ex vivo perfused graft (n = 17) were excluded from the study.

This retrospective study was approved by the local Institutional Review Board (code 17_2020) without the need for patient consent.

Data collection

Information on long-term follow-up was obtained from our institutional database and from patient charts, updated during regular post-HTx controls. The postoperative and long-term follow-up protocols used have been described in detail previously [11,12]. Particularly, coronary angiography was planned at 1-year post-HTx and every 2 years thereafter or whenever felt indicated. At each postoperative control right and left ventricular function and morphology were evaluated by transthoracic 2D echocardiography. During clinical evaluation, adherence to medical treatment was verified, and therapy was modified or titrated according to case-specific conditions.

Surgical technique and immunosuppressive treatment

Since 1999, the institutional protocol remained the same. Graft procurement and preservation were generally achieved by a combination of cold cardioplegic arrest and topical cooling and HTx was performed almost exclusively with the bicaval surgical technique. The first-line immunosuppression included cyclosporine, mycophenolate mofetil (MMF), and corticosteroids in all patients. All recipients received induction therapy with antithymocyte globulins, whenever possible.

A standardized protocol for corticosteroid withdrawal, within 6 months after HTx, and cyclosporine serum concentration lowering was applied guided by serial endomyocardial biopsies coupled with clinical and laboratory findings.

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Cyclosporine was replaced by tacrolimus in patients with persistent or repeated episodes of acute rejection despite immunosuppression optimization or in cases of cyclosporine side effects. Conversely, in cases of malignancies or CAV of grade ≥ 2, MMF was suspended and everolimus started as second-line drug treatment.

All patients received treatment with antiplatelet drugs and statins within 1 or 2 weeks after HTx according to their clinical condition.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median and interquartile range (Q1–Q3), according to data distribution after performing the Shapiro–Wilk test for normality. Categorical variables were expressed as absolute frequency and percentage. Continuous variables were compared with Student t-test or the Mann–Whitney U-test while categorical variables were compared with chi-square analysis or the Fisher exact test, as appropriate. Overall survival, freedom from CRAEs and from grade ≥ 2 CAV were estimated using the Kaplan–Meier approach and compared between the 2 groups with the log-rank test. Cox-regression model estimated factors independently associated with long-term mortality and freedom from CRAEs and grade ≥ 2 CAV. The multivariable Cox-regression analysis included covariates with $P < 0.10$ at univariate analysis and the variables that were significantly different at baseline among the 2 groups in order to control for potential confounders.

All statistics were performed using the Statistical Package for Social Sciences (SPSS) program (Chicago, IL, USA).

Results

Baseline characteristics

Out of 481 recipients undergoing HTx from 1999 to 2018, a total of 289 (60%) patients who received a graft evaluated with coronary angiography before the procurement were analyzed: 57 received a graft belonging to the CAD and 232 to the no-CAD Group. No cases of positive retrospective cross-matches were reported. As shown in Table 1, there were no significant differences in baseline characteristics between the two groups, except for an older donor age in CAD Group.

In CAD group, coronary atherosclerosis involved 2 or more coronary arteries in 37 grafts (65%) and/or the proximal or mid-portion of left anterior descending (LAD) artery in 31 (54%).

Immunosuppressive treatment was similar between the two groups up to 10 years (Appendix S1).

Early results

Of 30-day mortality was 5% ($n = 3$) and 9% ($n = 20$) for CAD and no-CAD groups, respectively ($P = 0.6$). Causes of early deaths are reported in Appendix S2.

Among postoperative complications, no differences between groups were observed considering the need for high inotropic support (inotropic score > 10) [13] or renal replacement treatment (RRT) and the need for post-HTx extracorporeal membrane oxygenation (ECMO) or intra-aortic balloon pump (IABP) support (Table 2).

Late survival

Mean follow-up time was 76 ± 56 and 75 ± 55 months for CAD and no-CAD Groups, respectively ($P = 0.8$). There were 89 (33%) late deaths: 15 in CAD (28%) and 74 (35%) in no-CAD Group. Causes of late mortality are reported in Appendix S2.

Actuarial survival at 5 and 10 years was 71 ± 6% and 62 ± 7% in CAD group and 71 ± 3% and 58 ± 4% in no-CAD Group ($P = 0.42$) (Fig. 1). Variables with $P < 0.1$ at univariate analysis were recipient age, diabetes mellitus, arterial hypertension, ischemic etiology, graft ischemic time and were combined with CAD group and donor age in multivariable analysis. Donor-transmitted atherosclerosis of grade ≤ moderate was not related to mortality at adjusted-multivariable analysis [HR 0.7 (95% CI 0.4–1.2]. Recipient age [HR 1.05 (95% CI 1.02–1.1)] resulted to be the only independent risk factor for late mortality.

Among CAD group, atherosclerotic involvement of ≥ 2 coronary arteries [HR 1.2 (95% CI 0.5–3.1)] or of the proximal or mid-portion of LAD [HR 0.8 (95% CI 0.3–2.0)] did not influence survival.

Three patients, all belonging to the no-CAD Group, underwent re-HTx after 1, 5, and 107 days because of graft failure.

CAV of grade ≥ 2

During follow-up, 47 patients in group no-CAD (20%) and 8 in group CAD (14%) developed a CAV of grade ≥ 2, diagnosed by means of coronary angiography and signs of allograft dysfunction [1].

Table 1. Recipients and donors baseline characteristics

Groups	no-CAD	CAD	*P* value
Recipient data			
No. of patients	232	57	-
Female sex, *n*. (%)	34 (15)	7 (12)	0.80
Age (years), median (Q1–Q3)	59 (53–64)	61 (53–65)	0.24
Creatinine (mg/dl), median (Q1–Q3)	1.3 (1.0–1.7)	1.3 (1.1–1.8)	0.89
Previous cardiac surgery, *n*. (%)	38 (16)	13 (23)	0.20
Ventricular assist device, *n*. (%)	18 (12)	2 (4)	0.20
Diabetes, *n*. (%)	56 (25)	18 (31)	0.07
ECMO, *n*(%)	25 (16)	3 (6)	0.09
Hypertension, *n*. (%)	81 (35)	23 (40)	0.50
Hypercholesterolemia, *n*. (%)	82 (35)	22 (38)	0.70
Ischemic etiology, *n*. (%)	79 (34)	21 (37)	0.70
Emergency heart transplantation, *n*. (%)	40 (17)	7 (12)	0.36
HT after 2010	118 (51)	32 (56)	0.55
Donor and Surgical data			
Age (years), median (Q1–Q3)	52 (46–57)	55 (49–59)	0.03
Female sex, *n* (%)	101 (43)	23 (40)	0.80
Causes of death			
Cerebrovascular event, *n*. (%)	216 (93)	56 (98)	0.84
Trauma, *n*. (%)	9 (4)	1 (2)	0.99
Anoxia, *n*. (%)	7 (3)	0 (0)	0.37
LVEF, median (Q1–Q3)	60 (60–65)	63 (60–67)	0.17
Cardiac arrest/severe hypotension, *n* (%)	21 (9)	4 (7)	0.45
Interventricular septum > 14 mm, *n* (%)	9 (4)	2 (4)	0.99
Drug abuse, *n* (%)	9 (4)	1 (2)	0.74
Smoke, *n*. (%)	9 (16)	32 (14)	0.67
Hypertension, *n*. (%)	6 (10.5)	21 (9)	0.8
Diabetes, *n*. (%)	2 (3.5)	11 (5)	0.99
Hypercholesterolemia, *n*. (%)	5 (9)	12 (5)	0.34
Lesions in 2 or more coronary vessels	--	37 (65)	
Lesions in proximal-mid LAD	--	31 (54)	
Graft ischemia time (min), mean ± SD	186 ± 58	188 ± 59	0.79

CAD = Coronary artery disease; ECMO: extracorporeal membrane oxygenation; LVEF: left ventricular ejection fraction; LAD: left anterior descending artery.

Freedom from grade ≥ 2 CAV was similar between the two groups, being 92 ± 2% and 81 ± 4% vs 93 ± 4% and 75 ± 8% at 5 and 10 years in no-CAD and CAD groups, respectively ($P = 0.93$) (Fig. 2a). Variables with $P < 0.1$ at univariate analysis were diabetes mellitus, arterial hypertension, ischemic etiology, hypercholesterolemia and were combined in the multivariable analysis with CAD group and donor age.

Donor-transmitted atherosclerosis of grade ≤ moderate was not related to the development of severe CAV [HR 0.9 (95% CI 0.4–2.0)] at adjusted-multivariable analysis, and no independent risk factors were detected.

Also, atherosclerotic involvement of ≥ 2 coronary arteries or the proximal or mid-portion of LAD did not affect development of high-grade CAV [HR 0.9 (95% CI 0.2–4.2)] and [HR 0.3 (95% CI 0.1–1.5)], respectively.

Among the 8 recipients of CAD group who developed grade ≥ 2 CAV, 4 exhibited progression of the disease in the sites of the lesions already present in the donor graft while 4 showed new lesions in other sites.

Proximal and focal stenoses [14 (6%) and 5 (9%)] of groups no-CAD and CAD were treated with percutaneous angioplasty and/or stenting ($P = 0.5$), after a median time from grade ≥ 2 CAV diagnosis of 1 day (range 1 day-9 years). Survival of these patients after revascularization was not statistically different than that of patients with grade ≥ 2 CAV lesions not amenable to be treated ($P = 0.11$, log-rank test).

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Table 2. Complications

Groups	No-CAD (n = 232)	CAD (n = 57)	P value
Postoperative, *n* (%)			
Mechanical ventilation > 72 h	33 (14)	9 (16)	0.8
Intra-aortic balloon pump	18 (8)	8 (14)	0.2
ECMO	7 (3)	2 (3.5)	0.7
IS > 10	57 (24)	20 (35)	0.1
Renal replacement therapy	20 (9)	5 (9)	0.9
TPM stimulation > 72 h	4 (2)	3 (5)	0.1
After discharge, *n* (%)			
CAV ≥ 2	47 (20)	8 (14)	0.7
CAV 3	*35 (15)*	*6 (10.5)*	
CAV 3 (with allograft dysfunction)	*5 (5)*	*2 (3.5)*	
PTCA	14 (6)	5 (9)	0.5
Permanent PM	14 (7)	7 (13)	0.15
Cardiac failure	16 (7.5)	5 (9)	0.8
AR episodes at 5 years	65 (28)	16 (28)	0.7
CMV infections at 5 years	39 (17)	8 (15)	0.8

ECMO = extracorporeal membrane oxygenation; IS = inotropic score; TPM = temporary pacemaker; CAV = cardiac allograft vasculopathy; AR = acute rejection; CMV = cytomegalovirus.

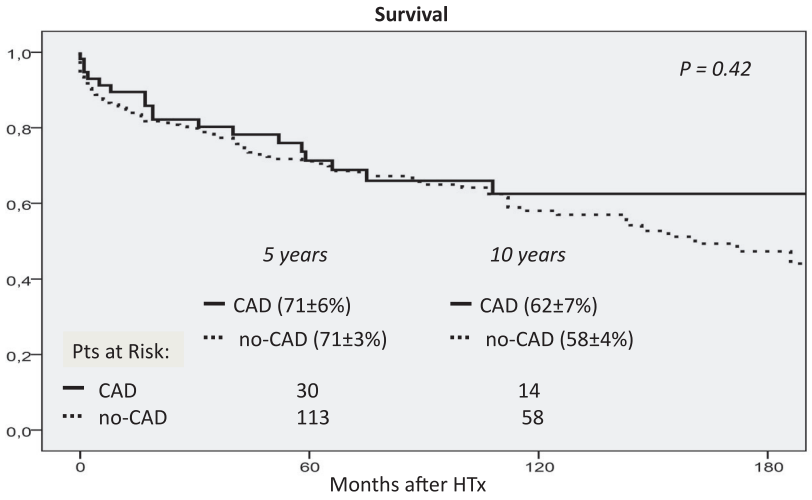

Fig. 1 Kaplan–Meier survival curves after heart transplantation according to presence (CAD) or absence (no-CAD) of graft coronary artery disease

CRAEs

Apart patients requiring percutaneous angioplasty (n = 19) and those requiring heart retransplantation (n = 3), a total of 21 patients required definite pacemaker implantation: 14 (7%) in no-CAD and 7 (13%) in CAD groups (P = 0.15). Patients requiring hospital re-admission for cardiac failure were 16 (7.5%) in no-CAD and 5 (9%) in CAD groups (P = 0.77). Cardiac-related deaths were 15 (6.5%) and 6 (10.5%) in groups no-CAD and CAD, respectively (P = 0.4).

Freedom from CRAEs at 5 and 10 years was 83 ± 3% and 66 ± 5% vs 84 ± 5% and 67 ± 9% in no-CAD and CAD Groups, respectively (P = 0.92) (Fig. 2b).

Variables with $P < 0.1$ at univariate analysis were recipient age, diabetes mellitus, ischemic etiology, hypercholesterolemia, HT after 2010, combined with CAD group and donor age in the multivariable analysis.

Donor-transmitted atherosclerosis of grade ≤ moderate was not related to the development of severe CAV [HR 0.95 (95% CI 0.5–1.83)] at adjusted-multivariable

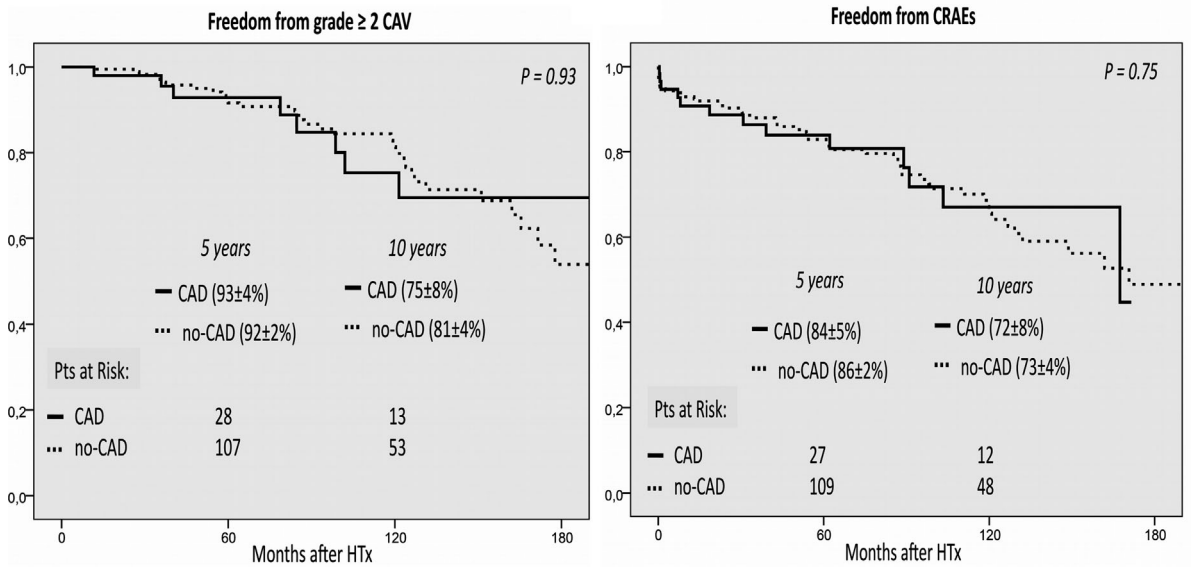

Fig. 2 (a) Kaplan–Meier curves representing Freedom from cardiac allograft vasculopathy of grade ≥ 2 after heart transplantation according to presence (CAD) or absence (no-CAD) of graft coronary artery disease. (b) Kaplan–Meier curves representing freedom from cardiac-related adverse events after heart transplantation according to presence (CAD) or absence (no-CAD) of graft coronary artery disease

analysis. Donor age [HR 1.03 (95% CI 1.001–1.07)] resulted to be the only independent risk factor CRAEs.

Among CAD group, atherosclerotic involvement of ≥ 2 coronary arteries or the proximal or mid-portion of LAD did not affect freedom from CRAEs [HR 1.6 (95% CI 0.5–5.4)] and [HR 0.3 (95% CI 0.1–1.3)], respectively.

Other complications

Rates of acute rejections and cytomegalovirus (CMV) infections at 5 years were similar (28% vs 24% and 15% vs 17%, $P = 0.7$ and 0.8 in no-CAD and CAD Groups, respectively). Acute rejection episodes and CMV infections did not affect development of severe CAV [HR 1.4 (95% CI 0.6–3.3)] and [HR 0.87 (95% CI 0.3–1.9)], respectively.

Discussion

In the attempt to expand the donor pool, the average age of heart donors is steadily increasing, particularly in Europe [2]. Although our institutional policy favors the matching of the older donor hearts with the older recipients, due to donor shortage the employment of older grafts has become widely considered as a standard option, also in younger recipients, and not necessarily in critical clinical condition [14]. Despite this trend may lead to a higher prevalence of preexisting donor coronary atherosclerosis, a largely adopted protocol aimed to detect and manage donor CAD is still lacking.

During donor evaluation, graft angiography is generally not a routine procedure resulting in 33% to 77% of donor hearts rejected based only on the presence of palpable calcification of the subendocardial coronary arteries [15]. Furthermore, it is still uncertain whether or not grafts evaluated with screening angiography and with proven coronary atherosclerosis should be utilized and which would be considered an acceptable upper limit of coronary stenosis [16-18].

Employment of donor hearts affected by less than severe atherosclerosis still represents an ongoing debate. In fact, the use of these hearts is considered with caution for the possibility of a greater susceptibility to early failure or to a more rapid progression of the preexisting CAD. For such reason, it appears important to determine which is the best method to detect and quantify coronary lesions at time of donor heart evaluation.

Graft CAD has been so far detected at the first coronary angiography performed after HTx. Schweigher et al. investigating the practice of coronary angiography in potential donor hearts found that this method was used in < 6% of donors evaluated at their institution [19]. These data led them to strongly recommend an implementation of angiographic studies to be an important part of the evaluation process of donor grafts.

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More recently, the detection of donor-transmitted coronary disease has been studied using intravascular ultrasound (IVUS) after HTx.

To our knowledge, the present study is the first one to present data on a significant number of donors ≥ 40 years of age undergoing pre-HTx coronary angiography as part of an evaluation of potential graft suitability. We consider this age limit as a threshold over which the use of specific tools to detect possible coronary lesions should be indicated. Once transplanted, we could assess the behavior of CAD in the donor heart, particularly in terms of stability, progression, or new onset of coronary lesions, by comparing pre- and post-HTx results of serial angiographic studies during periodical controls up to 10 years of follow-up (Appendix S3).

The results obtained indicate that, in the present experience, donor coronary lesions ≤ 50% did not represent a risk factor for poor outcome, both early and late survival of CAD and NCAD groups being similar at 10 years post-HTx. It is worth of note that CAD group was not affected by more early graft dysfunction, as suggested by the same rate of inotropic support, IABP, or ECMO required after HTx, and cardiac-related adverse events. Our results also confirm those reported by Li et al. who performed IVUS in 301 recipients 1 and 12 months and 3 years after HTx showing that donor CAD does not adversely affect survival up to 3 years [8].

More interestingly, this study shows that preexisting donor CAD did not accelerate its development to a more severe CAV, independently from the extension of the disease in the graft's coronary system and the involvement of the proximal or mid-portion of the LAD, and strengthen the concept of a predominant role of the immunological pathway in the onset of this complication. Our findings seem to be in contrast to those of previous studies [7-9] that suggested a correlation between donor-transmitted CAD and CAV. However, population characteristics, follow-up duration, and diagnostic modalities are very different from the present study and these factors might act as confounders.

When compared to coronary angiography, IVUS has definite advantages and is considered as the most important adjunctive tool in the hemodynamic laboratory setting [20-22]. Nevertheless, it also has definite limits represented by the possibility of many artifacts and acoustic shadowing which can interfere with image interpretation; furthermore, when compared to angiography, IVUS can examine only one artery at a time, only portions of an artery and not small branches [21].

In our experience, in contrast to IVUS, coronary angiography demonstrated to be a procedure which is easily available, less technically demanding, and less expensive and it is therefore feasible in almost every referring center. This diagnostic tool allows to avoid any false-positivity derived from coronary palpation whereas it easily detects any severe atherosclerotic lesions, defined as one or more major coronary vessels affected by a stenosis > 50 %; indeed, as recommended by ISHLT guidelines, such grafts should not be accepted for HTx, unless performing surgical revascularization at the time of implant [10,16]. Therefore, based on the present experience, our current protocol includes coronary angiography which we feel to suggest as routine procedure in all donors ≥ 40 years of age or in those with clear risk factors for CAD, as also supported by others [19,23].

The major limitation of this study is represented by its retrospective nature. However, this is a single-center study which, therefore, is not biased by differences in patient selection or treatments which might be present when including patients from other institutions.

Furthermore, the data analyzed were prospectively collected in a well-established institutional database which insures uniformity of data analysis thus providing, in our opinion, valuable results. It has also to be underlined that the immunosuppressive protocol employed in this series remained unchanged during the study period thus eliminating any potential influence of therapy variations on development of CAV. This study was based only on coronary angiography which still maintains the highest level of evidence and consensus opinion [1,3,16] for evaluating transplanted patients. We consider the high number of angiographic studies performed on a large heart donor population a strength of our paper which together with the long follow-up interval has provided meaningful data on a still controversial topic.

In conclusion, the results of our study indicate that employment of hearts from donors with less than severe CAD did not affect survival after HTx and did not accelerate the development of high-grade CAV. Our findings support the use of hearts with mild and moderate atherosclerotic disease providing beneficial effects in expanding the available donor pool. We favor the routine use of coronary angiography in the process of donor selection and recipients follow-up monitoring in the setting of HTx.

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The manuscript has not been published previously and it is not under consideration for publication elsewhere. A.L. and U.L. conceived the study idea and designed the study. A.L and V.F. collected data. Analysis was carried out by A.L. All authors participated in the discussion and interpretation of the results and are in agreement with the content of the manuscript.

Conflict of interest

The authors have no conflict of interest to declare.

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Disclosure

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Rates of immunosuppressive drugs administered among the CAD and no-CAD groups, at 1, 5 and 10 years after HTx.

Appendix S2. Causes of 30-day and late mortality

Appendix S3. A) Pre-procurement coronary angiography of a donor heart showing a <50% stenosis of the circumflex artery. B) Coronary angiography of the same heart 12 years after transplantation demonstrating absence of progression of the original lesion.

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