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Cardiac allograft vasculopathy in a long-term follow-up after heart transplantation: Role of remnant cholesterol in residual inflammation

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Abstract

Background: *Cardiac allograft vasculopathy (CAV) is a major prognosis limiting factor in heart transplantation (HTx). Disease development and progression are influenced by multiple determinants, but the role of remnant cholesterol (RC) in CAV has not yet been investigated. Therefore, the present study aimed to assess the prevalence of CAV in a very long-term follow-up after orthotopic HTx and to examine the role of RC in residual inflammation despite secondary prevention.*

Methods: *Herein, is a retrospective analysis of patient data collected at the last follow-up visit in an outpatient setting. Additionally, RC levels were calculated based upon cholesterol profile.*

Results: *The study population consisted of 184 patients with a mean follow-up of 15.0 ± 6.8 years. More than 40% of the overall cohort had CAV at last follow-up. The mean RC was 27.1 ± 14.7 mg/dL. Patients with CAV had significantly elevated RC despite intensified statin treatment ($p = 0.018$). A positive correlation was observed between RC and interleukin-6 as a marker of residual inflammation. Elevated RC and prolonged follow-up emerged as significant factors related to CAV in a multivariate analysis (odds ratio [OR] 2.9, 95% confidence interval [CI] 1.5–5.5, $p = 0.001$ and OR 3.3, 95% CI 1.4–7.7, $p = 0.006$, respectively), whereas mycophenolate mofetil was inversely associated with CAV (OR 0.4, 95% CI 0.2–0.9, $p = 0.034$).*

Conclusions: *Remnant cholesterol has proinflammatory properties and is associated with CAV development in HTx. Thus, RC should be concerned as an additional tool for risk assessment.* (Cardiol J 2022; 29, 5: 782–790)

Key words: cardiac allograft vasculopathy, remnant cholesterol, statin treatment, heart transplantation

Introduction

Cardiac allograft vasculopathy (CAV) is a relevant prognosis limiting condition in patients who have undergone heart transplantation (HTx) [1]. It is characterized by a diffuse involvement of the graft's coronary circulation, thus limiting the success of interventional treatment attempts. Research to elucidate the potential risk factors accelerating the CAV development has revealed that beyond the classic cardiovascular risk factors, immunological determinants and inflammation also

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contribute to disease progression [1–4]. Therefore, statin therapy is routinely recommended in all HTx patients, as it has been shown to have pleiotropic effects, to reduce CAV and to improve long-term outcomes regardless of lipid levels [5]. Nevertheless, recent data have revealed that remnant cholesterol (RC), composed of very low-density and intermediate-density lipoproteins in the fasting state, and additionally chylomicron remnants in the non-fasting state, is a relevant cardiovascular risk factor with proinflammatory properties. However, results regarding the efficacy of statin treatment in reducing RC levels remain inconsistent, and the effect of RC on CAV after HTx has not yet been assessed [6, 7].

Methods

Study design

This is a retrospective analysis of data collected at the most recent follow-up visit in the documented outpatient clinic for terminal heart failure and HTx. The patient population consisted of 268 cardiac transplant recipients, who were monitored and/or underwent HTx at this same institution. The time span between the first HTx and the last follow-up was 33 years (December 29th, 1987 – July 29th, 2021). Unfortunately, 80 patients were excluded because of insufficient data or clinical infection. In addition, 4 patients were not included as heart-lung-transplantation, retransplantation, and short-term follow-up (< 1 year) were considered exclusion criteria (Fig. 1).

The routine patient monitoring after HTx was based on on-site examinations in 3-month intervals. Available data on patient history, current complaints and dynamic of subjective symptoms, clinical and laboratory investigations were collected at every visit, whereas transthoracic echocardiograms were obtained every 6 months. The conducted results were thoroughly interpreted by experienced cardiologists. Based on the findings, additional tests were carried out if needed.

Laboratory parameters

The laboratory assessment consisted of complete blood count including lymphocyte subpopulations, lipid profile, coagulation results, basic liver and renal function panels, inflammatory parameters, N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) and serological examination to exclude subclinical infections. All measurements were performed in a fasting state. Additionally, RC levels were calculated using the formula:

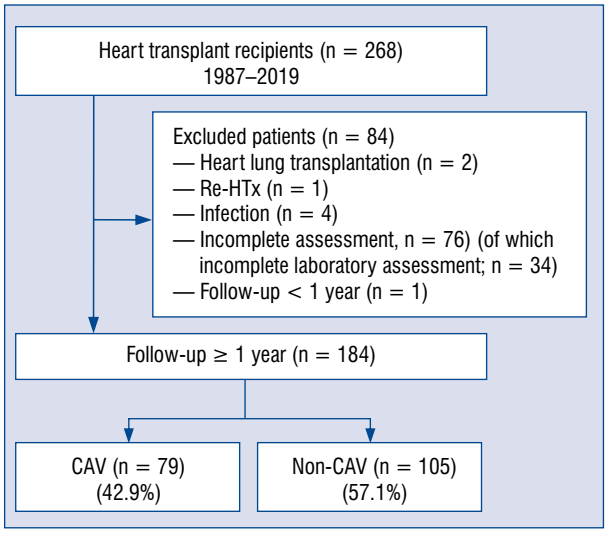

Figure 1. Flowchart of the study; HTx — heart transplantation; CAV — cardiac allograft vasculopathy.

RC = total cholesterol – low density lipoproteins cholesterol (LDL-C) – high density lipoproteins cholesterol (HDL-C). LDL-C was directly measured. Although the study population was treated with different statins in variable doses, most patients were on pravastatin. Therefore, to exclude possible bias related to statin dose, pravastatin equivalent dose (PED) was calculated.

Definition of CAV

Cardiac allograft vasculopathy was defined in accordance with the nomenclature of the International Society for Heart and Lung Transplantation. This classification is based on invasive coronary angiography (ICA) results in combination with an assessment of the cardiac allograft function. The recommendation to use primarily ICA is due to its universal availability and potential to provide the highest level of evidence. In contrast, the ability of intravascular ultrasound to deliver any additional diagnostic or therapeutic aid in CAV is considered limited, and optical coherence tomography is has not yet been incorporated in the diagnostic algorithm [1]. Therefore, the stratification of patients into two groups was performed according to whether CAV was present on any ICA in the time course after HTx: non-CAV (corresponding ISHLT CAV_0) and CAV group (≥ ISHLT CAV_1). Thus, the non-CAV group was comprised of patients without detectable angiographic lesions, and the CAV cohort encompassed subjects with any angiographically detectable stenoses, irrespective of the graft function (CAV_1, CAV_2, and CAV_3).

The study was performed in compliance with the Declaration of Helsinki and data sampling was approved by the local ethics committee (2019-021-f-S).

Statistical analysis

Statistical analysis was conducted using IBM SPSS Statistics software, version 27. Mean ± ± standard deviation was used to describe continuous variables and numbers (percentage) for categorical variables. Comparative assessment of parametric values was performed with Student t test and categorical variables with the χ^2 test. Two-tailed bivariate interactions were assessed with the Pearson correlation coefficient. The potential influence of risk factors was examined with the univariable proportional hazards model, and variables with $p < 0.1$ were introduced in a multivariable regression analysis with backward selection after assessment for collinearity. For all conducted analyses $p < 0.05$ was defined as statistically significant.

Results

Baseline characteristics

The study population consisted of 184 HTx recipients with a mean follow-up of 15.0 ± 6.8 years. More than 40% of the overall study population had CAV and the prevalence among survivors was almost 50% at 10-year follow-up (Fig. 2). No relevant differences were observed in the underlying etiology of terminal heart failure prior HTx between groups (Table 1). In particular, the ischemic nature of the antecedent disease was not more prevalent in the CAV population. Moreover, no relevant differences in past rejection episodes or rejections requiring therapy were found between the CAV and non-CAV groups (Table 1). Notably, the classic cardiovascular risk factors, except diabetes, had comparable prevalence in the two groups. Although the left ventricular ejection fraction (LVEF) was in the normal range in the population, patients with CAV had slightly more impaired LVEF, significantly elevated NT-proBNP, and a poorer functional class according to the New York Heart Association (NYHA) classification [8]. Additionally, cerebral/peripheral vascular disease (CAD/PAD) were more common in the CAV group (Table 1).

Medical treatment

Approximately 50% of the patients were on a cyclosporin A based immunosuppressive regime without significant differences between either group. Everolimus was more common in patients with CAV, whereas mycophenolate mofetil (MMF) was commonly used as a concomitant immunosuppressant in the non-CAV cohort. Comparative assessment of the medication revealed no relevant differences in the frequency of use of beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers. As a calcineurin sparing agent, diltiazem was a regular medication among one-third of the study population. Patients with CAV were more often on diuretics. More than 80% of the patients in both groups were taking statins with a higher intensity of the therapy in the CAV group. Ezetimibe was more commonly prescribed in the CAV group (Table 2).

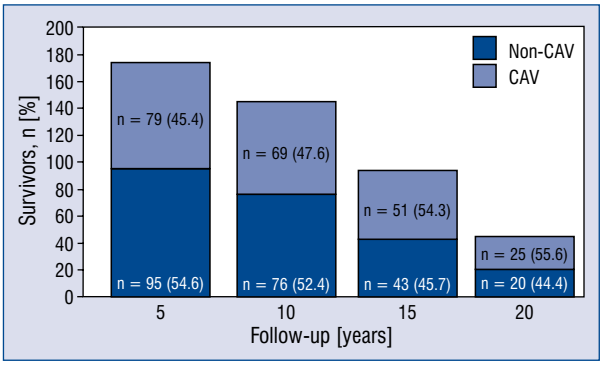

Figure 2. Prevalence of cardiac allograft vasculopathy (CAV) in survivors. Data are presented as number (percentage).

Lipid profile and inflammation

Since most of the patients were on statin treatment, there was no significant contrast between the LDL-C levels among both study groups. As depicted in Figure 3A–C, no differences were observed in the triglyceride (TGL) or HDL levels, except for in the RC values between the study groups. The mean calculated RC was 27.1 ± 14.7 mg/dL and was markedly higher in CAV. The assessment of the dose response to statin treatment, revealed a significant negative correlation of PED with the LDL-C levels ($p < 0.001$) but not with the absolute RC measures ($p = 0.818$) or with RC values exceeding 27 mg/dL ($p = 0.370$). Ezetimibe also had no influence on the RC levels in the same setting ($p = 0.934$ and $p = 0.505$, respectively). Moreover, the statin choice was not associated with the estimated RC levels ($p = 0.489$, when treated with atorvastatin, $p = 0.934$ with fluvastatin, $p = 0.157$ with pravastatin, $p = 0.657$ with rosuvastatin, and $p = 0.987$ with simvastatin). Notably, CAV had no influence on the statin preferences, but patients with CAV were on a more intensive statin treatment and is expressed as PED (Table 2).

Table 1. Characteristics of the patients at last follow-up.

Patient characteristics	Non-CAV	CAV	P
Demographics			
Age at HTx [years]	43.5 ± 16.7	46.4 ± 13.5	0.191
Follow-up [years]	13.6 ± 7.1	16.9 ± 5.9	0.001*
Male	84 (80.0%)	63 (79.9%)	1.000
Survivors	80 (76.2%)	56 (70.9%)	0.498
Antecedent disease			0.195
Ischemic cardiomyopathy	37 (35.2%)	29 (36.7%)	
Dilated cardiomyopathy	43 (41.0%)	41 (51.9%)	
Others	25 (23.8%)	9 (11.4%)	
Rejections			
Rejection episodes	59 (56.2%)	43 (54.4%)	0.881
Rejections requiring therapy	38 (36.2%)	30 (38.0%)	0.878
Clinical and laboratory examination			
Body mass index [kg/m^2]	26.0 ± 5.5	26.2 ± 5.4	0.776
Heart rate [bpm]	95.4 ± 90.0	82.0 ± 13.3	0.192
Systolic BP [mmHg]	126.0 ± 18.0	124.5 ± 18.9	0.588
Diastolic BP [mmHg]	79.4 ± 10.7	79.0 ± 10.9	0.824
NYHA class > 1	73 (69.5%)	66 (83.5%)	0.037*
NT-proBNP	3511.6 ± 6711.8	6104.7 ± 9033.1	0.034*
eGFR [mL/min/1.73 m^2]	49.3 ± 27.4	40.3 ± 23.2	0.109
Echocardiographic assessment			
LVEF [%]	58.4 ± 5.8	55.1 ± 9.2	0.006*
TAPSE [mm]	16.2 ± 3.6	16.4 ± 5.0	0.843
Comorbidities			
Arterial hypertension	83 (79.0%)	63 (79.7%)	1.000
Diabetes	26 (24.8%)	31 (39.2%)	0.038*
Dyslipidemia	89 (84.8%)	72 (91.1%)	0.261
End-stage-renal-disease	21 (20.0%)	14 (17.7%)	0.850
Precarcinoma/malinancy	29 (27.6%)	27 (34.2%)	0.419
Restrictive/obstructive lung disease	17 (16.2%)	15 (19.0%)	0.696
CAD/PAD	9 (8.6%)	17 (21.5%)	0.018*
Cytomegalovirus	15 (45.5%)	18 (54.5%)	0.174

Data are presented as mean ± standard deviation or number (percentage). HTx — heart transplantation; CAV — cardiac allograft vasculopathy; BP — blood pressure; NYHA class — functional assessment according to the New York Heart Association classification; NT-proBNP — N-terminal-pro hormone B-type natriuretic peptide; eGFR — estimated glomerular filtration rate; LVEF — left ventricular ejection fraction; TAPSE — tricuspid annular plane systolic excursion; CAD/PAD — cerebral/peripheral vascular disease; *p < 0.05

Furthermore, no differences were observed in routinely estimated levels of C-reactive protein (CRP) between both study groups, whereas interleukin-6 (IL-6) was significantly increased (Fig. 3A–C). Elevated RC (≥ 27 mg/dL) was associated with increased levels of IL-6 (IL-6 > 10 mg/dL, p = = 0.025). An RC level ≥ 27 mg/dL was identified as a significant factor associated with CAV in univariate and multivariate analyzes (Fig. 4).

Remnant cholesterol and CAV

Remnant cholesterol ≥ 27 mg/dL was also associated with CAV in a multivariate logistic regression analysis after adjustment for TGL, LDL-C, statin treatment and immunosuppressive regimes (odds ratio [OR] 2.6, 95% confidence interval [CI] 1.4–4.9, p = 0.003). As only a limited number of patients were treated with azathioprine (n = 6, 3.3% and there was only 1 subject without CAV),

Table 2. Medication.

	Non-CAV	CAV	P
Cardiovascular medication			
Beta-blockers	55 (52.4%)	52 (65.8%)	0.072
Calcium chanel blockers	28 (26.7%)	18 (22.8%)	0.608
Diltiazem	31 (29.5%)	22 (27.8%)	0.870
ACEI/AT II receptor antagonists	58 (55.2%)	47 (59.5%)	0.652
Diuretics except aldosterone antagonists	56 (53.3%)	59 (74.7%)	0.003*
Aldosterone antagonists	9 (8.6%)	15 (19.0%)	0.047*
Statins:	88 (83.8%)	64 (82.1%)	0.843
Atorvastatin	25 (23.8%)	29 (36.7%)	0.072
Fluvastatin	2 (1.9%)	2 (2.5%)	1.000
Pravastatin	49 (46.7%)	27 (34.2%)	0.098
Rosuvastatin	1 (1.0%)	1 (1.3%)	1.000
Simvastatin	10 (9.5%)	8 (10.1%)	1.000
Pravastatin equivalent dose [mg/d]	43.0 ± 52.1	62.0 ± 57.1	0.021*
Ezetimibe	6 (5.7%)	17 (21.5%)	0.003*
Platelet aggregation inhibitors	27 (25.7%)	62 (78.5%)	< 0.001*
Oral anticoagulants	14 (13.3%)	18 (22.8%)	0.116
Immunosuppressants medication			
Immunosuppressant:			
Cyclosporin A	58 (55.2%)	40 (50.6%)	0.554
Mycophenolate mofetil	91 (86.7%)	57 (72.2%)	0.016*
Everolimus	29 (27.6%)	36 (45.6%)	0.013*
Tacrolimus	26 (24.8%)	16 (20.3%)	0.485
Azathioprine	1 (1.0%)	5 (6.3%)	0.086
Prednisone	74 (70.5%)	55 (69.6%)	1.000

Data are presented as number (percentage). CAV — cardiac allograft vasculopathy; ACEI — angiotensin-converting enzyme inhibitors; AT II — angiotensin II; *p < 0.05

azathioprine was excluded from the analysis. The estimated r^2 in a linear regression analysis using the same model was 0.121 (p = 0.002).

The positive predictive value (PPV) of RC ≥ 27 mg/dL for CAV was 60.8% (p = 0.001), whereas no correlation for the TGL values exceeding 150 mg/dL was observed (PPV 48.1%, p = 0.174).

Additional factors

In addition to RC, IL-6, diabetes, and CAD/PAD emerged as associated with CAV in HTx. As expected, the disease prevalence was significantly higher in a prolonged follow-up. An assessment of the potential association of the immunosuppressive medication with CAV in a univariate analysis revealed a positive correlation with everolimus and an inverse association with MMF (Fig. 4A). However, the results regarding the immunosuppressive regime should be interpreted with caution, as most patients were treated with cyclosporin A, MMF, and prednisone in the first years after HTx, and the medication was changed in some cases in the time course of 15 years. Additionally, everolimus was recently the immunosuppressant of choice in the CAV group.

In a multivariate analysis RC, prolonged follow-up and MMF-based immunosuppression were the factors significantly associated with CAV development after adjustment for the remaining covariates (Fig. 4B).

Discussion

Under investigation was the association of RC with residual inflammation in patients with CAV in a very long-term follow-up after HTx. Additionally, the potential influence of secondary prevention through statin use on its serum levels was to be elucidated. According to available research, this is the first study to examine the role of the lipid remnants for the ischemic distress of transplanted hearts.

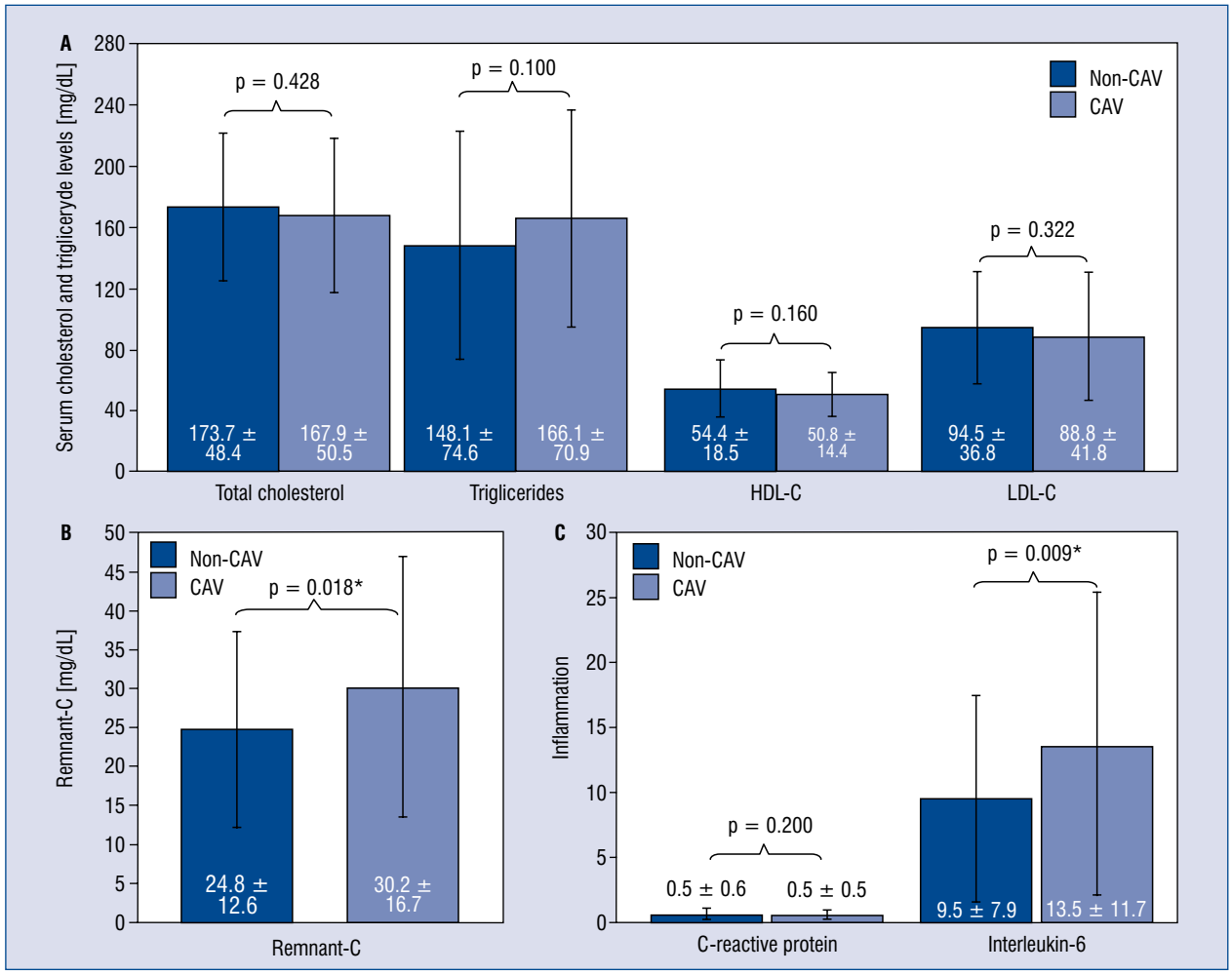

Figure 3. Serum cholesterol (**A**), remnant cholesterol (**B**) and inflammatory (**C**) parameters in cardiac allograft vasculopathy (CAV). Data are presented as mean ± standard deviation; Remnant-C — remnant cholesterol, HDL-C — high density lipoprotein cholesterol; LDL-C — low density lipoprotein cholesterol.

Disease prevalence

The burden of CAV among the survivors was increasing over the years after HTx, with a prevalence of 45.4%, 47.6%, 54.3% and 55.6% at 5, 10, 15 and 20 years, respectively (Fig. 2). Thus, the disease prevalence was higher at 5-year follow-up as previously reported, whereas the results at 10-year follow-up were consistent with available data [5]. A potential explanation for the present observations may be the difference in the diagnostic algorithms in follow-up. In accordance with the guidelines for adult HTx recipients, annual or biannual coronary angiographies were performed in the first years after HTx. If patients were free of CAV, less frequent invasive assessment was considered [5]. Thus, the results in long-term follow-up were often acquired during coronary angiographies conducted because of an acute coronary syndrome, cardiac decompensation, prior non-invasive assessment indicating ischemia, or clinical/laboratory results suggesting rejections. Additionally, CAV was diagnosed with ICA, which might have led to an underestimation in comparison to intravascular ultrasound or optical coherence tomography.

Underlying etiology

In assessing the influence of classic cardiovascular risk factors, both study groups were homogenous, except that diabetes and CAD/PAD were significantly more prevalent in CAV.

Previous research findings into the role of diabetes in CAV have been contradictory; whereas some studies have suggested that diabetes is not relevant, others have reported that it significantly influences CAV development and progression [9, 10]. In the current population, diabetics had

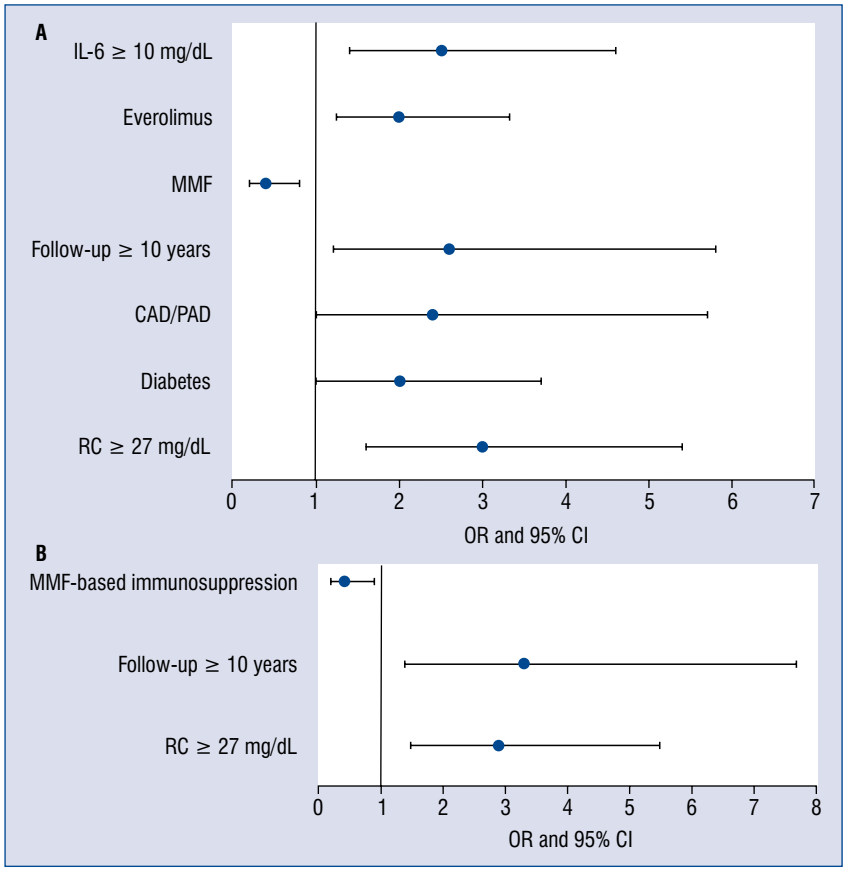

Figure 4. Factors associated with cardiac allograft vasculopathy; **A.** Univariate logistic regression analysis; **B.** Multivariate logistic regression analysis with stepwise backward selection; RC — remnant cholesterol; CAD/PAD — cerebral/peripheral vascular disease; MMF — mycophenolate mofetil; IL-6 — interleukin 6; OR — odds ratio; CI — confidence interval.

additionally elevated RC levels (RC ≥ 27 mg/dL, p = 0.026) and IL-6 (p = 0.023), revealing the possible interactions between metabolic factors and inflammation.

In addition, in line with previous findings, CAD and PAD were relevant concomitant diseases in CAV [11]. No routine sonographic screening was performed in the current patient population, resulting in a potential underestimation of disease prevalence. Ischemic cardiomyopathy before HTx was a significant predictor of CAD/PAD (OR 5.0, 95% CI 2.0–12.3, p < 0.001), and these patients more often had diabetes (p = 0.037). Thus, pretransplant predisposition to vascular disease may have consequences in posttransplant care, although no direct correlation between antecedent ischemic cardiomyopathy and CAV was observed.

Clinical consequences

As expected, patients with CAV had a more impaired left ventricular systolic function, thus resulting in significantly elevated NT-proBNP levels and consecutive functional impairment, expressed as NYHA functional class. In addition, CAV was associated with slightly more impaired renal function, although the difference was not statistically significant. The prevalence of end-stage renal disease was also comparable. Consequently, no relevant correlation was observed between the estimated glomerular filtration rate and NT-proBNP values. Therefore, the confounding effect of renal function on NT-proBNP and on patient functional status is limited and primarily CAV appears to cause the observed functional impairment.

Statins as a "panacea"

Most of the patients were on statin treatment, but only 28.8% of the overall study population attained the LDL-C target levels recommended by the 2016 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines for the management of dyslipidemias [12]. However, taking potential interactions with the immunosuppressants into consideration, the guidelines for

the care of heart transplant recipients recommend lower statin doses [5]. Furthermore, recent studies had reported a protective effect against CAV when a median LDL concentration of < 100 mg/dL was attained and no further benefit of a target concentration of < 70 mg/dL [13]. Additionally, as patients with CAV were on an intensified statin treatment, there were no significant differences between both study groups ($p = 0.189$), thus minimizing potential bias related to LDL-C values.

In contrast to findings from previous studies, there were no significant differences in CRP values between both patient groups and no relevant influence of statin treatment on its plasma levels was observed [14]. This finding may be attributable to retrospective character of the present study and the more intensive disease-modifying therapy in CAV. Herein, patients were clinically free of manifest infections. Thus, the estimated CRP levels were in the normal range or only slightly increased due to expected fluctuations. However, the IL-6 levels were remaining significantly elevated, thus indicating residual inflammation.

Kindling inflammation in CAV

Elevated IL-6 values (IL-6 ≥ 10 mg/dL) correlated with increased serum RC (RC ≥ 27 mg/dL, $p = 0.025$). This result is in line with previous findings reporting relevant inflammatory potential of RC and its role in atherosclerosis [6, 15]. Studies to date have shown that IL-6 is the strongest predictor of mortality among inflammatory parameters indicating that the future management of atherosclerosis may require inhibition of inflammation in addition to cholesterol-lowering. Additionally, IL-6 and CRP may continue to predict high cardiovascular risk, despite aggressive contemporary care including statin therapy, angiotensin inhibitors, beta-blockers, antithrombotic therapy, and high rates of coronary revascularization [16]. The limited predictive value of CRP in the present study may also be a consequence of the use of standard CRP measurements rather than high sensitivity CRP, thus potentially resulting in "mild" inflammation not being detected.

Additional factors

In a univariate analysis, everolimus and MMF-based immunosuppressive regimes emerged to be associated with CAV. Everolimus was previously reported to influence CAV development, and subsequent attempts to treat de novo coronary stenoses with everolimus-eluting stents which have shown promising results in short- and long-term follow-up [17–19]. In addition, MMF may also improve survival and be beneficial in CAV [20]. However, in our population, the benefits of the mentioned drugs, exceeding their immunosuppressive characteristics, were confirmed only for MMF. This finding might be explained by the retrospective nature of the study and the fact that most of the patients were on a cyclosporin A/MMF-based regimen for years and were lacking to experience the potential beneficial effect of the proliferation inhibitors due to short term follow-up. Additionally, given its protective effects, everolimus was recently the remedy of choice in CAV, thus limiting the predictive value of the immunosuppressive regime in an observational setting.

Future perspectives and treatment alternatives

When it comes to therapeutic alternatives against cholesterol remnants, PCSK9-inhibitors are known to reduce LDL-C levels and influence RC levels [21]. Unfortunately, none of the current patients were treated with PCSK-inhibitors, so evidence cannot be shown on their effectiveness. However, evidence in heart transplant recipients and data regarding their potential influence on CAV is still limited, and further results are expected to be announced in the coming years [22, 23].

Limitations and strength of the study

The major limitation of this study is its monocentric design, which limited the number of patients enrolled. However, the scarcity of donors and the volume of HTx should also be taken into consideration. The present study was based on a complete assessment in the relatively large cohort of 184 orthotopic heart transplant recipients and can deliver a solid base for further research to advance transplant care.

Additionally, the immunosuppressive regime was subject to change over the time course of 15 years after HTx according to the patients' clinical condition and commodities, limiting the predictive value of the data regarding the influence of the immunosuppressants in an observational setting. Therefore, these results should be interpreted with caution.

Conclusions

Cardiac allograft vasculopathy is a socially significant disease in HTx causing relevant functional impairment with increasing age. RC may effectively overcome the scope of the statins and promote inflammation in the coronary circulation of allografts, despite being largely overlooked in comparison to the far more prominent blood cho-

lesterol carriers. The estimation of RC requires no extra cost but can aid in residual risk assessment. Additionally, MMF had protective effects against CAV in long-term follow-up.

Conflict of interest: None declared

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