



Epicardial fat volume is related to the degree of cardiac allograft vasculopathy

Stefan Roest^{1,2} · Ricardo P. J. Budde^{1,3} · Jasper J. Brugts^{1,2} · Jan von der Thüsen^{2,4} · Theo van Walsum³ · Yannick J. H. J. Taverne^{2,5} · Felix Zijlstra¹ · Daniel Bos^{3,6} · Olivier C. Manintveld^{2,7}

Received: 20 January 2022 / Revised: 18 May 2022 / Accepted: 13 July 2022
© The Author(s) 2022

Abstract

Objectives Increasing evidence suggests a role for epicardial fat in the development of coronary artery disease in the general population. Heart transplantation patients are at increased risk of developing a specific form of coronary artery disease, cardiac allograft vasculopathy (CAV), which has far-reaching consequences in terms of morbidity and mortality. Until now, the role of epicardial fat volume (EFV) in the development of CAV remains unknown. Hence, we investigated the relationship between EFV and CAV as well as the influence of donor/recipient sex on EFV.

Methods Adult heart transplant patients who underwent coronary computed tomography angiography (CCTA) for CAV screening who were four or more years post-HT were included. Using the CT examinations, we quantified the EFV and the degree of CAV. Ordinal and linear regression models were used to assess the association of EFV with CAV.

Results In total, 149 (median age 44.5 years, 36% women) patients were included. The median time between HT and the CT scan was 11.0 (7.3–16.1) years. CAV grade 0, 1, 2 and 3 were seen in 85 (57%), 32 (22%), 14 (9%), and 18 (12%) patients, respectively. The median EFV was 208.4 (128.9–276.0) mL. Larger EFV were related to higher degrees of CAV (median of 164.7 to 290.6 mL for CAV grade 0 and 3, respectively, OR 5.23 (2.47–11.06), $p < 0.001$). Male recipients had significantly more EFV than female recipients irrespective of the donor sex (232.7 mL vs. 147.2 mL respectively, $p < 0.001$). Determinants for EFV were recipient sex, number of rejections, donor age, time between HT and CT scan, recipient BMI, and diabetes mellitus.

Conclusions EFV was associated with higher degrees of CAV. The recipient sex influenced the EFV more than the donor sex.

Key Points

- Patients after heart transplantation have a high amount of epicardial fat while larger amounts of epicardial fat are related to higher grades of cardiac allograft vasculopathy.
- Determinants of higher epicardial fat volume included recipient sex, number of rejections, donor age, time between HT and CT scan, recipient BMI, and diabetes mellitus.
- Longitudinal studies are needed to further disentangle the role of epicardial fat in the development and progression of cardiac allograft vasculopathy.

Keywords Cardiac allograft vasculopathy · Coronary computed tomography · Coronary artery disease · Epicardial fat · Heart transplantation

Daniel Bos and Olivier C. Manintveld contributed equally to this work.

✉ Olivier C. Manintveld
o.manintveld@erasmusmc.nl

¹ Department of Cardiology, Thorax Center, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands

² Erasmus MC Transplant Institute, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands

³ Department of Radiology and Nuclear Medicine, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands

⁴ Department of Pathology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands

⁵ Department of Cardiothoracic Surgery, Thorax Center, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands

⁶ Department of Epidemiology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands

⁷ Department of Cardiology, Thorax Center, Erasmus MC, University Medical Center Rotterdam, Room RG-431, Doctor Molewaterplein 40, 3015 GD, Rotterdam, The Netherlands

Abbreviations

CAD	Coronary artery disease
CAV	Cardiac allograft vasculopathy
CCTA	Coronary computed tomography angiography
CMV	Cytomegalovirus
EFV	Epicardial fat volume
GLP-1	Glucagon-like peptide-1 receptor
HT	Heart transplantation
HU	Hounsfield unit
ISHLT	International Society for Heart and Lung Transplantation
PCSK9	Proprotein convertase subtilisin/kexin type 9
SCCT	Society for Cardiovascular Computed Tomography
SGLT2	Sodium-glucose cotransporters-2

Introduction

Cardiac allograft vasculopathy (CAV) is a major complication after heart transplantation (HT), with a 10-year incidence of up to 50% [1]. CAV has far-reaching consequences and thereby exerts a huge contribution to morbidity and mortality [1]. CAV is an accelerated form of coronary artery disease, which is characterized by intima hyperplasia along the whole length of the coronaries [2–4]. The exact pathophysiology of CAV remains largely unknown; however, it is acknowledged that it is influenced by a combination of both immunological and non-immunological risk factors [2, 5].

Given the serious consequences of CAV and the fact that HT patients do not experience symptoms following ischemia due to the denervation of the heart, annual or biannual screening for CAV is advocated in the International Society for Heart and Lung Transplantation (ISHLT) guidelines [2]. Despite substantial drawbacks, such as high radiation dose and peri-procedural complications, the screening procedure is advised to be done with coronary angiography [2]. To overcome these drawbacks, at our institution, we successfully implemented coronary computed tomography angiographies (CCTAs) for routine screening of CAV in 2018 [6, 7]. Because CT scans contain much more information, beyond only luminal stenosis, which is assessed with invasive coronary angiography, CAV can be detected in an earlier stage of the disease [8].

In this light, specific interest has risen around the amount of epicardial fat, a layer of fat surrounding the coronaries that is situated between the myocardium and visceral pericardium [9]. Several studies have demonstrated that in the general population, people with larger amounts of epicardial fat have an increased risk for coronary artery disease (CAD) [10–16]. The effects of epicardial fat volume (EFV) even reach beyond CAD and are also linked to atrial fibrillation, heart failure with preserved ejection fraction, and larger amounts of

atherosclerosis [13, 17, 18]. Specifically in HT recipients, EFV may play an important role in the development of CAV, given its direct contact with the coronary arteries, and its excretion of pro-inflammatory factors [19, 20]. Currently, no studies have been performed to investigate the link between EFV and CAV. The primary aim of this study was to investigate the relationship between EFV and CAV. Furthermore, we investigated determinants of EFV in HT recipients and whether the donor and/or recipient sex has an influence on EFV.

Material and methods

All adult patients that were seen at our outpatient clinic and were more than 4 years post-HT who underwent a CT for annual/biannual CAV screening were included in the study. Patients with an impaired renal function (estimated glomerular filtration rate < 45 mL/min/1.73 m² before March 15, 2018, or < 30 mL/min/1.73 m² after March 15, 2018, due to a change in the contrast nephropathy prevention protocol at our institution) or iodine allergy were excluded from CCTA [6]. All first CT scans performed between February 2018 and June 2020 were included. CT scans in which CAV scores or epicardial fat volumes could not be determined were excluded from the analysis. Patients who underwent simultaneous organ transplantation (i.e., heart-lung transplantation) were excluded. The study was approved by the Medical Ethical Review Committee (MEC-2017-421) and conformed with the Declaration of Helsinki.

Assessment of epicardial fat

All scans were performed using the second- or third-generation dual-source CT scans (Somatom Definition Drive or Force, Siemens Healthineers) [6]. A scan consisted of a non-enhanced cardiac CT scan for coronary calcium scoring, followed by a CCTA. The non-enhanced CT was acquired at 120 kVp and reconstructed at 3-mm thick slices. The amount of epicardial fat was determined on the non-contrast enhanced scan. We used a validated custom-made algorithm that automatically delineated the pericardium [21]. Next, within the segmented pericardium, the EFV was determined by adding all voxels with Hounsfield unit (HU) thresholds between –200 and –30 and expressed in milliliters (mL) [21]. All regions smaller than 10 voxels were considered noise and not added to the total EFV (example in the graphical abstract) [21].

Assessment of CAV

The presence and severity of CAV were evaluated on CCTA according to the ISHLT guidelines by an experienced

cardiovascular radiologist with over 10 years' experience [4, 6]. However, since the ISHLT guidelines on CAV are based on coronary angiography findings and not on CCTA findings, a diameter stenosis grade of 50% instead of 70% was deemed significant as advised by the Society for Cardiovascular Computed Tomography (SCCT) [22]. The exact definition of CAV and other relevant definitions are mentioned in the [Supplemental Material](#).

Statistical analyses

The EFV was natural log-transformed in order to correct for the right-skewed, non-normal distribution. Using ordinal logistic regression models, we investigated the association between EFV and CAV. In the first model, we added EFV unadjusted. In the second model, we adjusted for sex and age of the recipient. In order not to overfit the statistical model, we computed propensity scores for each patient that captured all potential confounders of the association of EFV with CAV. This propensity score was used as covariable in model three and included the following variables: sex and age of the recipient, time since heart transplantation, BMI recipient at the CT scan, diabetes, smoking, number of rejections, CMV infection post-heart transplant, and ischemia time. Since hypertension (83%) and cholesterol lowering medication (89%) were very common in the study population, these could not be included in the model. We adjusted for recipient age in an attempt to capture unknown confounding factors in the recipient that may influence the association of EFV with CAV. Given the considerable, statistically significant correlation with donor age (Spearman's correlation: 0.59, $p < 0.001$), we did not include both ages (multicollinearity).

Next, using a linear regression model, we investigated determinants of EFV. First, a univariable analysis was performed including all potential determinants separately (listed below). Next, all variables that were associated with EFV with a p value ≤ 0.15 were simultaneously entered into a multivariable model. We specifically investigated associations of sex and age of the recipient, sex and age of the donor, number of rejections, time between HT and CCTA, prednisolone use, total cholesterol, low-density lipoprotein (LDL), BMI of the recipient, diabetes mellitus, and smoking post-HT with EFV. In order to investigate the effect of the sex of the recipient and the donor on the amount of epicardial fat, four groups were created (group 1, male recipient, male donor; group 2, male recipient, female donor; group 3, female recipient, male donor; group 4, female recipient, female donor). A Kruskal-Wallis test was performed to investigate the differences in median EFV per group. All statistical analyses were performed using IBM SPSS statistics 25 (IBM Corp.).

Results

In total, 249 patients more than four years post-HT were seen at the outpatient clinic during the study period. After exclusion criteria, 149 were included in the analysis. In Fig. 1, a flow-chart demonstrating the inclusion and exclusion of this study is demonstrated. Table 1 shows the characteristics of the study population ($n = 149$). The median age at the time of HT was 44.5 (28.0–53.6) years and 54 (36%) were female. The most frequent reason for HT was a non-ischemic cardiomyopathy (71%). Most of the donors were female (57%) and donors had a median age of 39.0 (21.0–48.5) years. The median time between HT and CT scan was 11.0 (7.3–16.1) years and

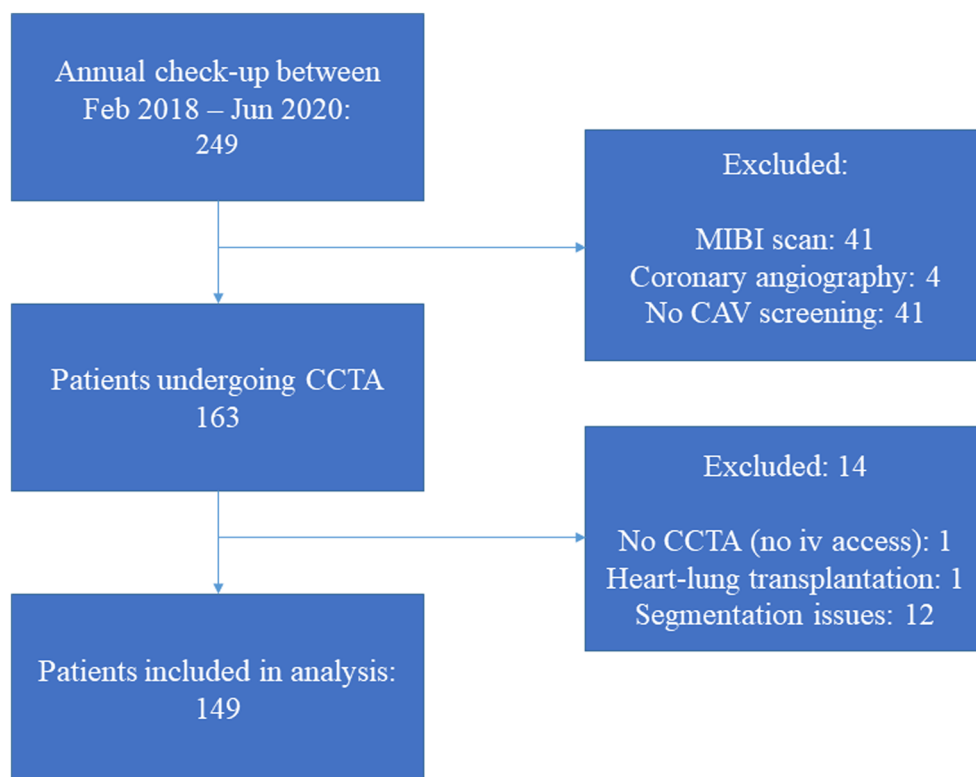
Table 1 Baseline characteristics of patients included in the study ($n = 149$)

Baseline characteristics	
Donor characteristics	
Age (years)	39.0 [21.0–48.5]
Female	85 (57)
BMI (kg/m ²)	23.5 ± 3.6
Recipient characteristics	
Female	54 (36)
Caucasian	126 (85)
Age at HT (years)	44.5 [28.0–53.6]
Ischemic CMP	44 (30)
Non-ischemic CMP	105 (71)
LVAD	22 (15)
Diabetes pre-HT	7 (5)
Creatinine at HT (μmol/L)	111 ± 44
Surgical data	
Ischemic time (min)	184 [153–216]
Data at the time of CT scan	
Time since HT	11.0 [7.3–16.1]
BMI (kg/m ²)	25.9 [23.5–28.8]
Number of rejections	1 [0–2]
CMV infection	44 (30)
Smoking post-HT	10 (7)
Diabetes mellitus	38 (26)
Hypertension	124 (83)
Immunosuppressive regimen	
Tacrolimus	128 (86)
Ciclosporin	20 (13)
Prednisolone	100 (67)

Continuous variables that are normally distributed are demonstrated as a mean ± standard deviation, non-normally distributed continuous variables as medians (25th–75th percentile (Interquartile Range)). Categorical variables are demonstrated with absolute numbers (percentages)

Abbreviations: *BMI*, body mass index; *CMP*, cardiomyopathy; *CMV*, cytomegalovirus; *CT*, computed tomography; *HT*, heart transplantation; *LVAD*, left ventricular assist device

Fig. 1 Flowchart demonstrating the in- and exclusion of patients in this study. Abbreviations: CAV, cardiac allograft vasculopathy; CCTA, coronary computed tomography angiography; iv, intravenous; MIBI, myocardial perfusion imaging



patients had a median of 1 (0–2) rejections. CMV infections occurred in 30% of patients.

Distribution of epicardial fat volume and prevalence of CAV

The median EFV on CT was 208.4 (128.9–276.0) mL. The overall prevalence of CAV was 43% of which 32 (22%) had CAV grade 1, 14 (9%) had CAV grade 2, and 18 (12%) had CAV grade 3. When stratified by CAV grade, the EFV ranged from a median of 164.7 to 290.6 mL for CAV grades 0 and 3, respectively (Fig. 2, $p < 0.001$).

Association of epicardial fat volume with CAV

We found a relationship between larger volumes of epicardial fat (per one unit increase of log-transformed EFV) with higher CAV grades (OR 5.23 (2.47–11.06), $p < 0.001$) (Table 2, model 1). Even after adjustments for sex and age of the recipient and a propensity score including risk factors for CAV, EFV was significantly associated with CAV (model 2: OR 5.17 (2.29–11.69), $p < 0.001$, model 3: OR 2.73 (1.01–7.41), $p = 0.049$). Additional models are demonstrated in Supplemental Table S1.

Determinants of epicardial fat volume

We found independent associations of sex of the recipient (β -0.36 (-0.51; -0.21), $p < 0.001$), the number of rejections (β 0.11 (0.05; 0.18), $p = 0.001$), donor age (β 0.01 (0.00; 0.01), $p = 0.008$), time between HT and CT scan (β 0.02 (0.01; 0.03), $p = 0.003$), BMI of the recipient at the time of the CT (β 0.04 (0.02; 0.05), $p < 0.001$), and diabetes

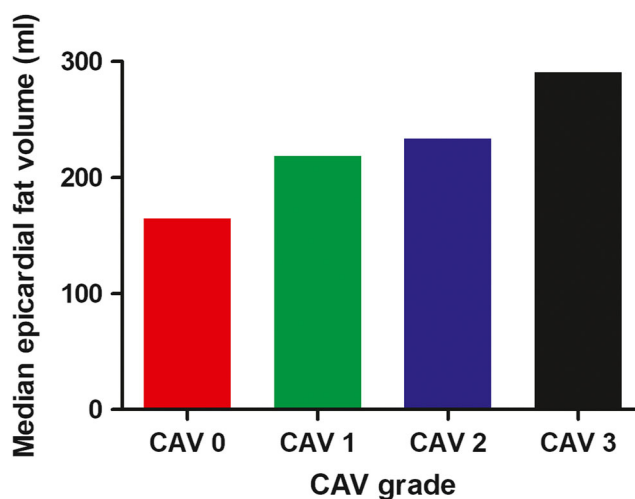


Fig. 2 The median epicardial fat volume stratified by cardiac allograft vasculopathy grade ($p < 0.001$). Abbreviations: CAV; cardiac allograft vasculopathy

Table 2 Ordinal regression analysis investigating the association between epicardial fat volume and cardiac allograft vasculopathy

	Cardiac allograft vasculopathy		
	OR (95% CI)		
	Model 1	Model 2	Model 3
Volume of epicardial fat*	5.23 (2.47–11.06)	5.17 (2.29–11.69)	2.73 (1.01–7.41)
<i>p</i> value	< 0.001	< 0.001	0.05**

Model 1: Unadjusted

Model 2: Adjusted for sex and age of the recipient

Model 3: Adjusted with a propensity score which included the following parameters: sex and age of the recipient, time since heart transplantation, BMI recipient at the CT scan, diabetes, smoking between heart transplantation and CT scan, number of rejections, CMV infection post-heart transplant, ischemia time

*Ln(epicardial fat volume) – transformed

***p* = 0.049

Abbreviations: *BMI*, body mass index; *CI*, confidence interval; *CMV*, cytomegalovirus; *CT*, computed tomography; *EFV*, epicardial fat volume; *OR*, odds ratio

mellitus (β 0.18 (0.03; 0.32), $p = 0.02$) with EFV in multi-variable analysis. All the included variables are displayed in Table 3. When specifically investigating the association between EFV and the number of rejections, we found larger volumes of epicardial fat with every rejection episode that occurred (Fig. 3, $p = 0.002$).

In the whole study population, 51 (34%) of the male recipient had a male donor, 44 (30%) of the male recipients had a female donor, 13 (9%) female recipients had a male donor, and 41 (28%) of the female recipients had a female donor. When the median EFV of male recipients is compared to the median EFV of female recipients, male recipients have a significantly higher EFV (232.7 mL vs. 147.2 mL respectively, p

< 0.001) irrespective of donor sex. The distribution of EFV per group is demonstrated in Fig. 4 ($p < 0.001$).

Discussion

Using a novel CCTA-based strategy for the follow-up of HT patients, we evaluated the amount of epicardial fat as a potential risk factor for CAV. We showed that patients post-HT have high epicardial fat volumes and that larger amounts of epicardial fat were associated with higher CAV grades even after correction for cardiovascular and transplantation-related risk factors. Furthermore, parameters that were related to an

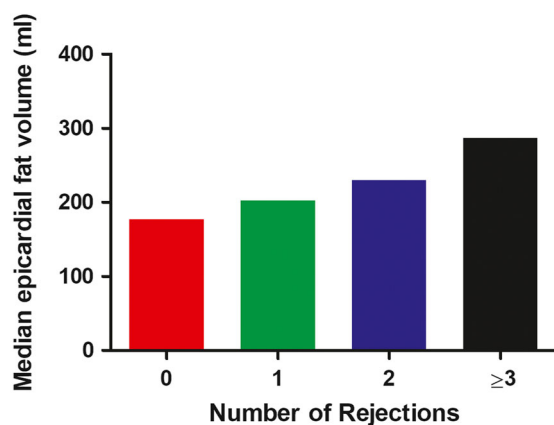
Table 3 Linear regression analysis to determine risk factors for Ln(epicardial fat volume)

	Univariable	<i>p</i> value	Multivariable	<i>p</i> value
Sex recipient (female vs male)	− 0.42 (− 0.58; − 0.27)	< 0.001	− 0.36 (− 0.51; − 0.21)	< 0.001
Age recipient	0.01 (0.01; 0.02)	< 0.001	0.00 (− 0.01; 0.01)	0.91
Sex donor (female vs male)	− 0.12 (− 0.29; 0.04)	0.15	− 0.04 (− 0.17; 0.09)	0.53
Age donor	0.01 (0.00; 0.01)	0.02	0.01 (0.00; 0.01)	0.008
Number of rejections *	0.14 (0.07; 0.22)	< 0.001	0.11 (0.05; 0.18)	0.001
Time between HT and CT	0.03 (0.01; 0.04)	< 0.001	0.02 (0.01; 0.03)	0.003
Prednisone use at CT	0.33 (0.16; 0.50)	< 0.001	− 0.01 (− 0.16; 0.14)	0.89
Total Cholesterol	0.12 (0.03; 0.20)	0.007	0.02 (− 0.13; 0.17)	0.81
LDL	0.13 (0.03; 0.23)	0.01	0.10 (− 0.07; 0.27)	0.24
BMI recipient at CT	0.06 (0.04; 0.07)	< 0.001	0.04 (0.02; 0.05)	< 0.001
Diabetes mellitus	0.27 (0.08; 0.45)	0.005	0.18 (0.03; 0.32)	0.02
Smoking post-HT	0.08 (− 0.13; 0.29)	0.43		

*(≥ 3 rejections combined as 1 group)

Regression coefficients of the (univariable and multivariable) linear regression analysis are demonstrated with 95% confidence intervals

Abbreviations: *BMI*, body mass index; *CT*, computed tomography; *HT*, heart transplantation; *LDL*, low-density lipoprotein



Number of patients: 46 44 37 21

Fig. 3 The median epicardial fat volume stratified by the number of rejections post-heart transplantation ($p = 0.002$)

increased EFV were: the male sex of the recipient, the number of rejections, the age of the donor, the time between HT and CT scan, the BMI of the recipient, and diabetes mellitus. Male recipients had significantly more EFV compared to female recipients, irrespective of the donor sex.

To our knowledge, this is the first study investigating the association between EFV and CAV. EFV may play an important role in the development of CAV, especially given the near proximity of epicardial fat to the coronary arteries, and its excretion of pro-inflammatory factors [19, 20]. This is further corroborated by recent evidence stating that epicardial fat could play a role in the formation of CAV due to lymphocytes [5, 19]. Lymphoid nodules have been demonstrated in the epicardial fat post-HT [19, 23]. These nodules get organized and attract T-cells. Moreover, epicardial adipocytes secrete more pro-inflammatory (IL-6, IL-8) than anti-inflammatory cytokines (adiponectin), especially in diabetic and obese

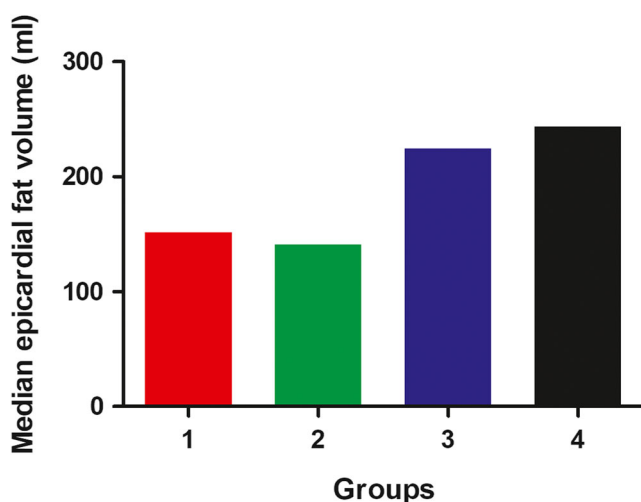


Fig. 4 The median epicardial fat volume stratified by recipient/donor sex ($p < 0.001$). Group 1: female recipient, female donor; group 2: female recipient, male donor; group 3: male recipient, female donor; group 4: male recipient, male donor

patients [19]. Further basic science studies are needed to confirm this association in heart transplantation recipients.

In our study, the median EFV was 208.4 (128.9–276.0) mL. When comparing this EFV to large population studies such as the Framingham Heart Study, the Heinz Nixdorf Recall cohort, the EISNER study and the Rotterdam study, the EFV in these studies was significantly lower (mean of 122 mL, 86 mL, 89 mL, and a median of 102 mL, respectively) [10–13]. In the Heinz Nixdorf Recall cohort, the population was divided into quartiles with a mean EFV in the highest quartile of 151 mL [11]. This demonstrates that patients post-HT have a tremendous amount of epicardial fat compared to the general population and could possibly explain why these patients experience CAV early post-HT [1, 2].

EFV was significantly associated with CAV in our study which is in line with results from atherosclerosis studies demonstrating a higher risk of atherosclerosis in patients with higher EFV [10–14, 16]. Risk factors for CAV include not only donor age, recipient sex, acute rejections, and time since HT but also traditional cardiovascular risk factors such as diabetes mellitus, hypertension, and hypercholesterolemia [1, 4, 5, 24]. Some of these factors were associated with EFV in our study. This could clarify how some risk factors are associated with CAV. One example in this perspective is the sex of the recipient. Male recipients are more likely to develop CAV than female recipients [1]. The reason for this is not fully understood but could be explained by neurohormonal differences between sexes. We have demonstrated that male recipients have a higher amount of epicardial fat, irrespective of the sex of the donor, which could explain the increased incidence of CAV in male recipients. The question that still needs to be answered is whether the effects of the risk factors associated with CAV are via epicardial fat or whether these risk factors have an effect on CAV both directly as well as indirectly via epicardial fat. For example, rejection episodes are a known risk factor for CAV [5, 24]. Possibly, rejections of the cardiac allograft can induce adjustments to the endothelium in the coronaries, inducing CAV. Another pathway could be that the EFV is increased due to the inflammatory environment during a rejection episode and/or the high prednisolone dosage that is frequently given to treat acute rejections. It is well known that patients who use prednisolone have an increased amount of body fat [25]. A study investigating the impact of steroid therapy on epicardial fat depositions found that patients with a rheumatic disorder who were on chronic steroid therapy had significantly more EFV than patients without steroid therapy [26]. Moreover, patients with high dosage steroid therapy also had more EFV than patients on low dose steroid therapy [26]. This could at least partially explain the increased amount of epicardial fat in HT recipients and could hint towards the cumulative effect that prednisolone has on EFV (daily dosage as well as the high dosages given during rejection).

Currently, no specific treatment option for CAV is available. Two of the main treatments to date for CAV are statins (recommended for all patients post-HT) and mTOR-inhibitors (everolimus and sirolimus) [2]. Everolimus and sirolimus are mostly given to patients who are longer post-HT in whom early stages of CAV have been identified. Even though mTOR-inhibitors could halt the progression of CAV in some patients, the side effects make it impossible to start these drugs in all patients [27]. Even in patients with CAV, it is sometimes discontinued due to the side effects. The association between EFV and CAV found in this study raises the question of whether EFV could be a new target for drug therapies in order to delay CAV development. Several studies have been performed to reduce EFV in the general population. It has been demonstrated that weight loss with a very-low calorie diet, intensive training session, and even bariatric surgery reduces EFV [28]. It is however questionable whether this can also be applied to HT recipients who sometimes have serious comorbidities [1]. With the introduction of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, sodium-glucose cotransporters-2 (SGLT2) inhibitors, and glucagon-like peptide-1 receptor (GLP-1) agonists more treatment options are becoming available for patients with cardiovascular disease. In the general population, SGLT2 inhibitors and GLP-1 agonists have demonstrated that they could reduce EFV [29–31], while PCSK9 inhibitors have been proposed as a potential drug to reduce EFV [32, 33]. In a recent study investigating a mouse HT model, the authors found a significant reduction in the amount of inflammation and development of CAV after treatment with a GLP-1 agonist [34]. Even though the authors did not investigate the EFV in these mice, the reduction in inflammation (and possibly the development of CAV) could be explained by the reduction in EFV. Recently, several case series and small cohort studies have examined the safety of the abovementioned drugs in the HT population [35, 36]. Studies are now needed to confirm that EFV can be reduced in HT patients and whether this could slow down CAV progression.

Our study has several limitations. Our study is a single-center study which comes with its limitations, even though the study sample was not small. Furthermore, most patients in our population were Caucasian, so whether our results can be extrapolated to other ethnicities is uncertain. Patients with a contrast allergy or an impaired renal function (eGFR < 30 mL/min/1.73 m²) had no CCTA (but stress scintigraphy) for CAV screening which could alter our results. No CCTA was performed shortly after HT which is why a comparison with baseline measurements is not possible. However, it is to be expected that the baseline EFVs are comparable or even lower compared to general population studies such as the Framingham and the Rotterdam Study [12, 13], which makes our results even more interesting. We were not able to correct for all risk factors related to CAV, such as donor age, hypertension, and hypercholesterolemia due to the fact that these

were related too highly related to other factors or too prevalent in the study population. Furthermore, it was not possible to correct the calcium score, as in patients with a stent, the calcium score could not be determined. This was the case in a significant number of patients with a higher CAV grade. Lastly, CCTA has limitations to describe the CAV grade. The CAV grade classification is based on angiographic findings [4]. In contrast to angiography findings, significant stenosis on CCTA is a stenosis > 50% instead of 70% (Supplemental Material). This could lead to an overestimation of the CAV grade in this study. On the other hand, patients can have abnormalities in the coronary wall, not protruding into the lumen, leading to a CAV grade 0 based on the guidelines, even though abnormalities are seen [8]. Additional studies need to be performed to explore whether patients with a high EFV also have an increased risk to have CAV progression. This could help identify high-risk patients who need more close monitoring and more aggressive treatment of their comorbidities to slow down CAV progression.

In conclusion, we demonstrated that the EFV is significantly increased in HT recipients compared to the general population (even more in male recipients). Larger volumes of epicardial fat were significantly associated with higher CAV grades. Parameters associated with an increased EFV include the sex of the recipient, donor age, rejections, time since HT, the BMI of the recipient, and diabetes mellitus. Further studies are needed to investigate whether the reduction of EFV could slow down the progression of CAV, improving quality of life and survival.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00330-022-09029-2>.

Funding The authors state that this work has not received any funding.

Declarations

Guarantor The scientific guarantor of this publication is Olivier C. Manintveld.

Conflict of interest The authors of this manuscript declare relationships with the following companies: R.B. has received institutional support from Siemens, is a board member of the ESCR and a member of the SCCT guidelines committee. J.J.B. has received speaker's fees or advisory board fees from Abbott, Bayer, and Boehringer Ingelheim not related to this work. O.M. has received fees for Advisory board meetings of Astra Zeneca, Boehringer Ingelheim, and Novartis not related to this work. Furthermore, he is Chair of the working group Heart Failure of the Dutch Society of Cardiology (unpaid). All other authors have declared no conflicts of interest.

Statistics and biometry One of the authors has significant statistical expertise.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Study subjects or cohorts overlap Some study subjects or cohorts have been previously reported in:

Nous FMA, Roest S, van Dijkman ED et al (2021) Clinical implementation of coronary computed tomography angiography for routine detection of cardiac allograft vasculopathy in heart transplant patients. *Transpl Int*

And:

Budde RPJ, Nous FMA, Roest S et al (2021) CT-derived fractional flow reserve (FFR_{ct}) for functional coronary artery evaluation in the follow-up of patients after heart transplantation. *Eur Radiol*.

However, both studies had a different study population than this study (this study is larger in size) and these articles were written for a different research question/purpose.

Methodology

- retrospective
- cross-sectional study
- performed at one institution

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

References

1. Khush KK, Cherikh WS, Chambers DC et al (2019) The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-sixth adult heart transplantation report - 2019; focus theme: donor and recipient size match. *J Heart Lung Transplant* 38:1056–1066
2. Costanzo MR, Dipchand A, Starling R et al (2010) The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. *J Heart Lung Transplant* 29:914–956
3. Avery RK (2003) Cardiac-allograft vasculopathy. *N Engl J Med* 349:829–830
4. Mehra MR, Crespo-Leiro MG, Dipchand A et al (2010) International Society for Heart and Lung Transplantation working formulation of a standardized nomenclature for cardiac allograft vasculopathy-2010. *J Heart Lung Transplant* 29:717–727
5. Pober JS, Chih S, Kobashigawa J, Madsen JC, Tellides G (2021) Cardiac allograft vasculopathy: current review and future research directions. *Cardiovasc Res* 117:2624–2638
6. Nous FMA, Roest S, van Dijkman ED et al (2021) Clinical implementation of coronary computed tomography angiography for routine detection of cardiac allograft vasculopathy in heart transplant patients. *Transpl Int* 34:1886–1894
7. Budde RPJ, Nous FMA, Roest S et al (2021) CT-derived fractional flow reserve (FFR_{ct}) for functional coronary artery evaluation in the follow-up of patients after heart transplantation. *Eur Radiol* 32:1843–1852
8. Foldyna B, Sandri M, Luecke C et al (2020) Quantitative coronary computed tomography angiography for the detection of cardiac allograft vasculopathy. *Eur Radiol* 30:4317–4326
9. Dey D, Nakazato R, Li D, Berman DS (2012) Epicardial and thoracic fat - noninvasive measurement and clinical implications. *Cardiovasc Diagn Ther* 2:85–93
10. Nakanishi R, Rajani R, Cheng VY et al (2011) Increase in epicardial fat volume is associated with greater coronary artery calcification progression in subjects at intermediate risk by coronary calcium score: a serial study using non-contrast cardiac CT. *Atherosclerosis* 218:363–368
11. Mahabadi AA, Berg MH, Lehmann N et al (2013) Association of epicardial fat with cardiovascular risk factors and incident myocardial infarction in the general population: the Heinz Nixdorf Recall Study. *J Am Coll Cardiol* 61:1388–1395
12. Rosito GA, Massaro JM, Hoffmann U et al (2008) Pericardial fat, visceral abdominal fat, cardiovascular disease risk factors, and vascular calcification in a community-based sample: the Framingham Heart Study. *Circulation* 117:605–613
13. Bos D, Shahzad R, van Walsum T et al (2015) Epicardial fat volume is related to atherosclerotic calcification in multiple vessel beds. *Eur Heart J Cardiovasc Imaging* 16:1264–1269
14. Bettencourt N, Toshke AM, Leite D et al (2012) Epicardial adipose tissue is an independent predictor of coronary atherosclerotic burden. *Int J Cardiol* 158:26–32
15. Nagayama Y, Nakamura N, Itatani R et al (2019) Epicardial fat volume measured on nongated chest CT is a predictor of coronary artery disease. *Eur Radiol* 29:3638–3646
16. Mancio J, Azevedo D, Saraiva F et al (2018) Epicardial adipose tissue volume assessed by computed tomography and coronary artery disease: a systematic review and meta-analysis. *Eur Heart J Cardiovasc Imaging* 19:490–497
17. Bos D, Vermooij MW, Shahzad R et al (2017) Epicardial fat volume and the risk of atrial fibrillation in the general population free of cardiovascular disease. *JACC Cardiovasc Imaging* 10:1405–1407
18. van Woerden G, Gorter TM, Westenbrink BD, Willems TP, van Veldhuisen DJ, Rienstra M (2018) Epicardial fat in heart failure patients with mid-range and preserved ejection fraction. *Eur J Heart Fail* 20:1559–1566
19. Baldwin WM 3rd, Halushka MK, Valujskikh A, Fairchild RL (2012) B cells in cardiac transplants: from clinical questions to experimental models. *Semin Immunol* 24:122–130
20. Chatterjee TK, Stoll LL, Denning GM et al (2009) Proinflammatory phenotype of perivascular adipocytes: influence of high-fat feeding. *Circ Res* 104:541–549
21. Shahzad R, Bos D, Metz C et al (2013) Automatic quantification of epicardial fat volume on non-enhanced cardiac CT scans using a multi-atlas segmentation approach. *Med Phys* 40:091910
22. Leipsic J, Abbara S, Achenbach S et al (2014) SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. *J Cardiovasc Comput Tomogr* 8:342–358
23. Wehner JR, Fox-Talbot K, Halushka MK, Ellis C, Zachary AA, Baldwin WM 3rd (2010) B cells and plasma cells in coronaries of chronically rejected cardiac transplants. *Transplantation* 89:1141–1148
24. Spitaleri G, Farrero Torres M, Sabatino M, Potena L (2020) The pharmaceutical management of cardiac allograft vasculopathy after heart transplantation. *Expert Opin Pharmacother* 21:1367–1376

25. Liu D, Ahmet A, Ward L et al (2013) A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. *Allergy Asthma Clin Immunol* 9:30
26. Kitterer D, Latus J, Henes J et al (2015) Impact of long-term steroid therapy on epicardial and pericardial fat deposition: a cardiac MRI study. *Cardiovasc Diabetol* 14:130
27. Arora S, Andreassen AK, Karason K et al (2018) Effect of everolimus initiation and calcineurin inhibitor elimination on cardiac allograft vasculopathy in de novo heart transplant recipients. *Circ Heart Fail* 11:e004050
28. Rabkin SW, Campbell H (2015) Comparison of reducing epicardial fat by exercise, diet or bariatric surgery weight loss strategies: a systematic review and meta-analysis. *Obes Rev* 16:406–415
29. Sato T, Aizawa Y, Yuasa S et al (2018) The effect of dapagliflozin treatment on epicardial adipose tissue volume. *Cardiovasc Diabetol* 17:6
30. Iacobellis G, Villasante Fricke AC (2020) Effects of semaglutide versus dulaglutide on epicardial fat thickness in subjects with type 2 diabetes and obesity. *J Endocr Soc* 4:bvz042
31. Braha A, Timar B, Diaconu L et al (2019) Dynamics of epicardial fat and heart function in type 2 diabetic patients initiated with SGLT-2 inhibitors. *Diabetes Metab Syndr Obes* 12:2559–2566
32. Dozio E, Ruscica M, Vianello E et al (2020) PCSK9 Expression in epicardial adipose tissue: molecular association with local tissue inflammation. *Mediators Inflamm* 2020:1348913
33. Antoniades C, Kotanidis CP, Berman DS (2019) State-of-the-art review article. Atherosclerosis affecting fat: what can we learn by imaging perivascular adipose tissue? *J Cardiovasc Comput Tomogr* 13:288–296
34. Wang Z, Wang M, Hu X et al (2019) Liraglutide, a glucagon-like peptide-1 receptor agonist, attenuates development of cardiac allograft vasculopathy in a murine heart transplant model. *Transplantation* 103:502–511
35. Sammour Y, Nassif M, Magwire M et al (2021) Effects of GLP-1 receptor agonists and SGLT-2 inhibitors in heart transplant patients with type 2 diabetes: Initial report from a cardiometabolic center of excellence. *J Heart Lung Transplant* 40:426–429
36. Jennings DL, Jackson R, Farr M (2020) PCSK9 inhibitor use in heart transplant recipients: a case series and review of the literature. *Transplantation* 104:e38–e39

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.