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Heart rate and early progression of cardiac allograft vasculopathy: A prospective study using highly automated 3-D optical coherence tomography analysis

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Abstract

Introduction: Heart rate slowing agents are frequently prescribed to manage heart transplant (HTx) patients with the assumption that higher heart rate is a risk factor in cardiovascular disease.

Patients and Methods: This prospective two-centre study investigated early progression of cardiac allograft vasculopathy (CAV) in 116 HTx patients. Examinations by coronary optical coherence tomography and 24-hour ambulatory ECG monitoring were performed both at baseline (1 month after HTx) and during follow up (12 months after HTx).

Results: During the first post-HTx year, we observed a significant reduction in the mean coronary luminal area from 9.0 ± 2.5 to 8.0 ± 2.4 mm² ($p < 0.001$), and progression in mean intimal thickness (IT) from 106.5 ± 40.4 to 130.1 ± 53.0 μ m ($p < 0.001$). No significant relationship was observed between baseline and follow-up mean heart rates and IT progression ($R = 0.02$, $p = 0.83$;

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Disclosure statement

The authors have no conflicts of interest to disclose.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

$R=-0.13$, $p=0.18$). We found a mild inverse association between beta blocker dosage at 12 months and IT progression ($R=-0.20$, $p=0.035$).

Conclusion: Our study did not confirm a direct association between mean heart rate and progression of CAV. The role of beta blockers warrants further investigation, with our results indicating that they may play a protective role in early CAV development.

Keywords

cardiac allograft vasculopathy; heart rate; beta blocker; optical coherence tomography

INTRODUCTION

Heart transplantation (HTx) is accompanied by sympathetic and parasympathetic denervation, which typically results in increased heart rate (HR) due to negation of the vagus nerve effect¹. Several epidemiological studies have demonstrated that faster HR is a risk factor for cardiovascular diseases, including coronary artery disease²⁻⁴. Faster HR results in decreased shear stress, leading to stimulation of mechanoreceptors located on the surface of the endothelium and upregulation of proatherogenic genes⁵, effects that can lead to endothelial dysfunction and affect graft outcomes^{5,6}. However, reports on the relationship between elevated HR and cardiac allograft vasculopathy (CAV) development have reported contradictory and inconsistent results⁷⁻¹⁰. All the studies published on the subject suffer from significant limitations, mainly due to retrospective analysis, the use of coronary angiography as a CAV imaging modality, and the use of single ECG recording as a HR rate analysis tool⁷⁻¹⁰. Our aim was to perform a large prospective study using highly automated optical coherence tomography (OCT) image analysis and 24-hour ECG monitoring as a means of elucidating the relationship between HR and early progression of CAV.

METHODS

Patients

Between October 2014 and March 2017, 116 subjects, who survived first 12 months after HTx, from the Heart Centre at IKEM, Prague, Czech Republic and the Centre of Cardiovascular and Transplantation Surgery, Brno, Czech Republic were enrolled. The study (clinical trial NCT02503566) complies with the Declaration of Helsinki and was approved by the respective ethics committees. All HTx recipients 18 years of age were deemed eligible for inclusion in the study provided they were able and willing to give their informed consent. Exclusion criteria included chronic kidney disease stage IV (glomerular filtration <30 mL/min), unfavourable post-HTx clinical conditions, such as episodes of severe rejection or nosocomial sepsis with prolonged antibiotic treatment during the first month, ongoing need for circulatory support using a ventricular assist device, and acute allograft failure.

Coronary angiography in donors was indicated according to our institutional protocol in men >45 years, and in women >50 years. Coronary angiography was also considered in case of abnormal ECG or echocardiogram, and in case of significant cumulation of risk factors for ischemic heart disease.

ECG monitoring

All patients were continuously monitored during the first month after HTx using ECG telemetry system, which allowed precise 24/7 assessment of HR and/or arrhythmias. 24-hour ECG Holter monitoring was performed twice under standardized conditions (during a hospital stay) at 1 month (M1) after HTx, shortly before the first post-surgical discharge, and at 12 months after HTx (M12).

24-hour ECG Holter recordings were performed using the GE MARS Ambulatory ECG Analysis System (Prague centre) and the Philips Zymed Holter Recorder (Brno centre). The following variables were assessed: mean, maximal, minimal HR, and the total number of atrial and ventricular premature complexes.

Heart rate slowing medication

Patients in our cohort were started on bradycardic medication within the first month after HTx solely at the discretion of the attending physician based on HR, and/or presence of any forms of tachyarrhythmias. The choice and dose of drugs was not prespecified. Patients were given either beta blockers (metoprolol or bisoprolol) and/or ivabradine. HR-slowing (non-dihydropyridine) calcium channel blockers were not administered. All patients were continuously monitored during the first month after HTx using ECG telemetry system, which allowed precise 24/7 assessment of heart rate, and/or arrhythmias. Likewise, during all follow-up visits within the first post-HTx year, bradycardic medication was titrated depending on resting ECG findings.

If bradycardic medication was administered, patients were given either beta blockers (metoprolol or bisoprolol) or ivabradine. For the purpose of analysis, the daily dose of bisoprolol was multiplied by a factor of 20 to obtain the metoprolol-equivalent dosage¹¹.

Blood pressure monitoring and treatment

Everyday measurement of blood pressure under standardized conditions was performed during first month after HTx. Subsequently, blood pressure was routinely assessed during mandatory visits within the first post-HTx year. To tackle arterial hypertension, patients were treated with three main antihypertensive medications – ACE-inhibitors (ramipril, perindopril), dihydropyridine calcium channel blockers (amlodipine, lercanidipine) and beta blockers.

OCT method

Coronary OCT imaging was performed at M1 and M12 after HTx as part of routine surveillance cardiac catheterisation using a commercial intracoronary OCT system (ILUMIEN/DRAGONFLY OPTIS, St. Jude Medical, St. Paul, MN). A 54 mm-long segment of each HTx patient's left anterior descending (LAD) artery, located within a proximal 100 mm segment, was imaged using automated pullback at 18 mm/sec and 10 frames/mm. Where the LAD artery exhibited unfavourable anatomical characteristics (small calibre, extreme tortuosity, muscle bridge), a 100 mm-long proximal segment of the left circumflex (LCx) or the right coronary artery (RCA) was imaged. Baseline and follow-up OCT-imaged segments mutually overlapped.

Image interpretation

For each frame of all OCT pullbacks, luminal, intimal, and medial surfaces were automatically segmented using a fully three-dimensional LOGISMOS graph-based approach developed at the University of Iowa,^{12,13} as previously documented^{14,15}. Boundaries were identified as OCT brightness changes showing tissue interfaces between adjacent wall layers. Automatically identified borders were efficiently edited using our Just-Enough-Interaction method adapted for the OCT segmentation environment^{16,17}. This technique allows segmentation errors to be corrected in a 3D fashion on a regional basis, an alternative to contour-by-contour/frame-by-frame manual retracing. This highly accurate, multi-layer model ensures quantitative CAV analysis of every frame of the imaged vessel for both baseline and follow-up image pullbacks. After identifying corresponding vascular landmarks, baseline and follow-up pullback pairs were co-registered, enabling location-specific and fully three-dimensional comparisons of layer-based changes using quantitative indices. Our 3D OCT layer analysis was presented in Figure 1, showing example cross-sectional OCT frames from baseline and follow-up image pullbacks together with IT map for a typical non-progression and progression pullback pairs.

Quantitative descriptors

Branches and ambiguous areas of the wall were excluded from analysis based on the consensus of two expert cardiologists. Full frames were excluded when appearing in only one of the two registered pullbacks.

The luminal, intimal, and medial layers for each frame were segmented and analysed to obtain average thickness and area measurements. The intima-to-media ratio was calculated for each frame of the analysed pullbacks by dividing frame-specific average intimal thickness (IT) by frame-specific average medial thickness. Mean intimal thickening (IT) was determined as the average difference between IT at M1 and M12 for all co-registered vessel wall locations. While IT can also be assessed locally, the reported IT has always been averaged over the entire registered segment in this work. Maximal intimal thickening was determined as the maximal value of segmental intimal thickening, comparing all 3mm-long segments of the vessel wall. Our 3D OCT layer analysis is presented in Figure 1, showing example of cross-sectional OCT frames from baseline and follow-up image pullbacks together with IT map for a typical non-progression and progression pullback pairs.

The cohort was divided into two groups based on IT observed during the first post-HTx year: a non-progression group (70% of patients, IT $\leq$ 0.028 mm) and a progression group (30% of patients, IT > 0.028 mm). The threshold of IT = 0.028 mm was selected arbitrarily with respect natural clustering of the patient cohort.

Statistical analysis

Numerical variables were described as mean values $\pm$ standard deviations or median and interquartile ranges (IQR), where appropriate. The coronary morphological changes or patient characteristics changes from M1 to M12 were evaluated using Paired Student's t-test or Wilcoxon signed-rank test, where appropriate. Categorical variables, presented as counts

and percentages, were compared using Fisher's exact test. Spearman's rank correlation coefficient was used to evaluate the relationship between 12-month IT progression and HR-related variables. The generalised linear model was used to examine the association between donor age and HR in the presence of HR-slowness medication. Bonferroni correction was used to avoid false positives where several tests were performed simultaneously. R environment was employed for statistical computing, with a P-value of 0.05 used to denote statistical significance.

RESULTS

In total, 116 out of 121 originally recruited patients, were enrolled into the study (5 patients died prior to M12 follow-up visit). Patient characteristics are summarised in Table 1. In this population, 97 left anterior descending (LAD), 7 left circumflex (LCx), and 12 right coronary (RCA) arteries were analysed.

Cohort analysis

Based on the 116, M1–M12 pairs of registered OCT pullbacks, the median analyzable angular range was 264° (IQR 234–286°) per frame. No full frames were excluded after image registration; the median overlapping pullback length was 38.7 mm. A total of 43,012 registered frame pairs were analysed, resulting in an average co-registered intimal surface area of 239.7 mm² per vessel pullback; local descriptors were available for an average of 78,617 co-registered wall locations per pullback.

During the first post-HTx year, we observed highly significant reduction in the mean coronary luminal area and increase in all indices related to IT (Table 2).

By separation the cohort into the non-progression and progression subgroups (with IT dichotomy of 0.028 mm), we did not identify any significant CAV predictor among all patient-based, donor-related characteristics and non-immunological risk factors (Table 3).

Table 4 summarises 24-hour ECG Holter findings at M1 and M12 after HTx. No significant relationships were found between IT and either baseline or follow-up Holter-based variables (Table 5).

Associations between HR-slowness medication and IT at M12 after HTx are given in Table 6. There were no significant differences in IT between treated and non-treated patients. However, we observed a mild inverse association between beta blocker dosage at 12 months and IT ($R=-0.20$, $p=0.035$). It is well known that mean heart rate inversely correlates with donor age early after HTx ($R=-0.26$, $p<0.01$ at M1 in our cohort). This probably resulted in escalation of beta blocker therapy in patients after HTx from younger donors. Consequently, beta blocker dosage correlated with donor age even more tightly ($R=-0.41$, $p<0.0001$) at M12. However, donor age itself was not related to IT, i.e. development of CAV. Also, recipient age was unrelated to both beta blocker dosage and IT.

DISCUSSION

The principal findings of our study can be summarised as follows: (1) there was significant progression of IT as early as within 12 months after HTx; (2) increased HR was not associated with early CAV development; (3) higher doses of beta blockers at 12 months after HTx are possibly a protective factor in IT progression.

CAV-related graft failure accounts for the majority of patient mortality within 5 to 10 years, surpassing the contributions of malignancies and infections^{18,19}. Rapid development of CAV is diagnosed in a high proportion of HTx patients, occurring as early as within one year after the index procedure^{15,18}. Early identification of such patients is of extreme importance, since it can favourably affect CAV-related allograft failure rates and the subsequent need for re-transplantations¹⁹. Furthermore, elevated resting HR after HTx might be an independent, and relatively easily modifiable, risk factor for the development of CAV or other systemic cardiovascular diseases²⁰.

Rapid development is a hallmark of CAV, with major changes in IT typically observed within year 1, less so in subsequent years²¹. After registering overlapping baseline and follow-up images of OCT pullbacks, we were able to axially and rotationally match 387 frames (IQR: 321–438) per pullback on average. We detected significant intimal thickening as early as within one year after HTx, a finding in agreement with previous studies^{18,21}. We want to stress out that our analysis is not using maximal intimal thickening – rather we employ intimal thickening averaged over the entire pullback length. Most of all previous studies illustrated CAV in a very simple manner, as they chose the thickest single site intimal thickness from the whole pullback as a CAV surrogate. Compared to those studies, our highly accurate and sophisticated 3D OCT analysis, enabled us to evaluate progression of IT frame by frame. Hence, we report detailed and accurate information about diffuse CAV progression of the whole vessel, as this approach better characterizes pattern of this disease.

Despite the significant early IT progression observed in our relatively large cohort of 116 patients, no significant risk factors of CAV development were identified in respect of selected donor-related characteristics or non-immunological risk factors. This confirms the indisputable role of immune mechanisms in CAV development, such as donor-specific anti-HLA antibodies^{10,22}, which are particularly prevalent in early stages of CAV disease and characterised by diffuse concentric fibrous intimal hyperplasia²³. Traditional cardiovascular risk factors contribute to the CAV progression rather in the later stages of CAV development (beyond 1 year after HTx), which are characterized by the diffuse incorporation of lipids into the vessel wall and resemble classical processes in ischaemic heart disease²⁴.

Autonomic denervation during the HTx procedure results in altered electrophysiological properties of the transplanted heart. During parasympathetic denervation, suppression of sinoatrial node automaticity is eliminated, and tachycardia becomes a typical post-HTx clinical feature¹. Several mechanisms have recently been proposed as potentially responsible for various tachycardia-related detrimental effects. An elevated HR enhances the magnitude and frequency of the tensile stress imposed on the arterial wall and prolongs the exposure of coronary endothelium to the systolic low and oscillatory shear stress⁶. Consequently,

causing arterial wall injury and endothelial cell dysfunction. In atherosclerotic phenotypes of coronary vessels, a faster HR increases the risk of plaque rupture and contributes to coronary thrombosis^{1,4}.

Current data on the effects of increased resting HR on all-cause mortality in HTx patients and CAV development is contradictory. While there is relatively uniform evidence of tachycardia-related effects on mortality^{5,25–27}, the impact on CAV development is less clear^{7–10}. Due to small sample sizes, retrospective and observational approaches, and overall design, previous studies^{7–9} have failed to produce convincing data on the role of tachycardia in CAV development. Such efforts are particularly hampered by the use of low-resolution coronary angiography as an imaging modality for CAV assessment and a reliance on single ambulatory ECG recordings for HR analysis. In contradiction to previous studies on this topic, recent data published by Liebo et al.¹⁰ reveal that a HR >95 beats/min 1 year after HTx is associated with increased incidence of CAV. In this context, the results of our prospective study – utilising 24-hour ECG Holter monitoring for HR assessment and OCT imaging for detailed and precise analysis of early IT – are of major importance.

Our 24-hour ECG Holter monitoring results showed no significant changes in paired examinations. The one exception was maximal HR, which increased over time despite increased doses of bradycardic medication, perhaps indicating more vigorous activity of patients, or partial re-innervation as early as within one year after HTx. According to evidence from Awad et al.²⁸, sympathetic re-innervation occurs within 5 to 6 months after HTx, mostly appearing in the left ventricular and sinoatrial node regions of the allograft.

None of our 24-hour ECG Holter variables, including mean HR, were associated with IT 12 months after HTx. This finding thus refutes the hypothesis that high HR is involved in the development of CAV.

The association we observed between younger donor age and higher HR at M1 after HTx is in agreement with previous studies^{9,10}. A likely explanation for such a finding is sinus node dysfunction, which increases in prevalence during ageing and commonly occurs in older adults, as demonstrated by the decline in intrinsic HR²⁹.

Despite its detrimental effect on the exercise capacity of HTx patients³⁰, beta-blocker treatment might be of benefit. Compared to other studies^{5,26}, a relatively high proportion of patients in our cohort were prescribed beta blockers (51.7 % at M1, 66.4 % at M12). There are three possible explanations for this: (1) Assumption that increased HR predicts worse outcomes in cardiovascular disease^{5,25–27} could be associated with over-prescription of beta blockers to achieve resting HR <95–100/min; (2) Favoured beta blockers for the treatment of symptomatic atrial ectopy which can be indirectly suggested by higher frequency of atrial premature complexes on 24-hour ECG Holter observed at 1 month in patients treated with beta blockers; (3) Preference of beta blockers in combination treatment of arterial hypertension.

Interestingly, higher doses of beta blockers at 12 months after HTx were weakly associated with lower IT progression. We did not identify any factor that could indirectly be responsible for this relationship. Padilla et al. demonstrated that activation of the sympathetic nervous

system leads to an immediate alteration in retrograde shear stress, which is associated with decreased endothelial function³¹. Their findings lend further weight to our speculation that the direct sympatholytic effect of beta blockers may play a role in preventing CAV development. In light of the negative association between higher HR and CAV progression, the role of beta blockers certainly warrants further investigation.

Study limitations

1. Our HTx patients were treated with beta blockers at the discretion of the attending physician based on HR, presence of any forms of arrhythmias, and hypertension. A randomised study would have been better in assessing HR effects on CAV progression.
2. Relatively high number of patients were treated with bradycardic medication. Our reliance on this treatment may have resulted in the narrow range of HR, possibly reducing the power of the study to detect the relationship between HR and CAV development.
3. First OCT imaging results were only available at M1 after HTx. Thus, we were unable to differentiate between donor-transmitted coronary artery disease and de novo progression of CAV during the first post-HTx month. Due to the additional need to administer angiographic contrast and the associated risk of renal function deterioration, only one vessel per patient was examined by OCT. Due to the limited depth of OCT tissue penetration (1.5 to 3 mm), layered coronary structures, especially the external elastic lamina, were not always visible in some patients with extensive donor-transmitted coronary disease, thus impacting on our ability to precisely detect changes in the coronary vasculature.
4. The patients with CAV progression were defined by arbitrary increase in mean intima thickness > 0.028 mm. At this stage of research, we can only rely on information about very early IT changes. The decision to use the 70%–30% split of the groups was motivated by the well-known percentages of long-term CAV effects without claiming that the same patients who demonstrate early IT thickening will ultimately be the same as those with advanced CAV later.

CONCLUSIONS

Our prospective 2-centre trial using highly automated 3D graph-based OCT analysis did not confirm a direct association between mean HR and 12-month progression of CAV. Nevertheless, the role of HR-slowng medication such as beta blockers warrants further investigation, with our results indicating that they may play a protective role in early CAV development.

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Figure 1: OCT layer analysis in 3D

OCT layer analysis in 3D, showing example cross-sectional OCT frames from baseline and follow-up image pullbacks together with IT thickness maps and a map showing IT changes (ΔIT) for a typical non-progression (a, b, c, top) and a typical progression (d, e, f, bottom) image pullback pairs. (a,d) Cross-sectional OCT frames from a baseline (M1) pullback sequence – original and intimal & medial layer segmentation. (b,e) Corresponding OCT frame from the follow-up (M12) pullback, axially and rotationally registered. In (a,d) and (b,e) panels, white wedges depict automatically-identified exclusion regions in which layer thickness measurements are not possible; e.g., due to guidewire shadows (6 o'clock in (a,b); 11 o'clock in (d,e)), vessel branches (6–8 o'clock in (d,e)), imaging artifacts, or limited penetration depth of the OCT imaging modality. (c,f) Feature maps of baseline IT, follow-up IT, and intimal thickening (ΔIT) shown for the entire OCT pullback length as a color-coded vessel wall layer thickness, cylindrical vessel wall is shown in an unwrapped fashion. Baseline and follow-up maps are mutually registered and the shadowed areas represent non-measurable exclusion regions shown as wedges in the (a,b) panels.

Table 1

Patient characteristics

	Baseline (n=116)	Follow up (n=116)	p-value
Age (years)	50.3±12.5		-
Men	90 (78%)		-
Ischaemic cardiomyopathy	23(20%)		-
Cold ischaemia time (min)	125 (±50.2)		-
Donor age (years)	41.2 (±11.7)		-
Donor gender (men)	79 (68%)		-
Explosive brain death	86 (74%)		-
BMI (kg/m2)	26.2 (±4.2)	28.7 (±4.6)	<0.001
CMV infection within 12 months		13 (11%)	
Mild rejection within 12 months		87 (75%)	
Severe rejection * within 12 months		23 (20%)	
Humoral rejection within 12 months		3 (3%)	
Systolic blood pressure (mmHg)	125.9 (±15.9)	127.2 (±13.7)	0.41
Diastolic blood pressure (mmHg)	78.5 (±8.8)	80.7 (±9.0)	0.025
Hemoglobin level (g/L)	111.0 (±12.8)	131.8 (±15.7)	<0.001
LV ejection fraction (%)	61.1 (±4.1)	61.0 (±4.8)	0.85
Total cholesterol	4.90 (±1.10)	4.27 (±1.08)	<0.001
HDL (mmol/l)	1.51 (±0.42)	1.23 (±0.44)	<0.001
LDL (mmol/l)	2.68 (±1.08)	2.29 (±0.84)	<0.001
TAG (mmol/l)	1.55 (±0.67)	1.75 (±1.09)	0.07
HbA1C (mmol/mol)	40 (±7.8)	46.4 (±16.9)	<0.001
Aspirin	68 (59%)	80 (69%)	0.13
Statin	92 (79%)	99 (85%)	0.42
Steroids	116 (100%)	97 (84%)	<0.001
Tacrolimus	112 (97%)	112 (97%)	1
Cyclosporin A	4 (3.4%)	4 (3.4%)	1
mTOR inhibitor (everolimus)	0 (0%)	11 (10%)	<0.001
Mycophenolate mofetil	113 (97.4%)	81 (69.8%)	<0.001
Beta blockers	60 (51.7%)	77 (66.4%)	0.032
Metoprolol	50 (43.1%)	61 (52.6%)	
Bisoprolol	10 (8.6%)	16 (13.8%)	
Ivabradine	2 (1.7%)	16 (13.8%)	0.001
ACE-inhibitors	22 (19%)	30 (26%)	0.20
Dihydropyridine calcium channel blockers	28 (24%)	39 (34%)	0.08
ACE-inhibitors + Dihydropyridine calcium channel blockers	7 (6%)	16 (13.8%)	0.047

BMI – body mass index; CMV – cytomegalovirus; HTx – heart transplant; LV – left ventricle; M – month;

min – minutes; mTOR – mammalian target of rapamycin; TAG - triacylglycerols

*
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Table 2

Optical coherence tomography findings

	M1 after HTx	M12 after HTx	Change (M12 - M1)	P-value (after Bonferroni correction)
Mean luminal area (mm ²)	9.0±2.5	8.0±2.4	-1.0±1.5	<0.001
Mean intimal thickness (µm)	106.5±40.4	130.1±53.0	23.6± 30.3	<0.001
Maximal intimal thickness (µm)	174.5±92.3	223.3±106.9	79.1±71.3	<0.001
Mean medial thickness (µm)	82.2±22.0	83.7±21.2	1.5±11.7	1
Mean intimal+medial thickness (µm)	188.7±58.6	213.8±70.2	25.1±37.7	<0.001
Max intimal+medial thickness (µm)	274.3±107.7	324.5±122.0	87.0±79.3	<0.001
Mean intimal/medial ratio	1.4±0.3	1.6±0.4	0.3±0.3	<0.001

HTx – heart transplant; M – month; mm – millimetres; µm – micrometres

Table 3

Predictive factors of CAV progression, with the patient cohort divided into quartiles based on IT progression 12 mo after HTx

	Non-progression (70 %) n=81	Progression (30 %) n=35	P-value (after Bonferroni correction)
Patient age (years)	50.9±12.7	49.3±12.2	1
Men (%)	78	77	1
History of ICMP (%)	21	17	1
Donor age (years)	39.7±12.0	44.4±10.5	1
Donor gender (men) (%)	68	63	1
Cold ischaemia time (min)	137±55	129±52	1
Explosive brain death (%)	74	68	1
Mild rejection (%)	72	83	1
Severe rejection * (%)	16	29	1
Humoral rejection (%)	4	3	1
CMV infection (%)	10	14	1
Systolic blood pressure (mmHg) M1/M12	126.7±16.6	124.1±14.3	1/1
	126.8±14.2	127.9±12.8	
Diastolic blood pressure (mmHg) M1/M12	78.5±8.5	78.6±9.4	1/1
	80.4±9.6	81.3±7.7	
BMI (kg/m2) M1/M12	26.4±3.9	25.9±5.0	1/1
	29.1±4.4	27.4±4.9	
Total cholesterol (mmol/l) M1/M12	4.79±1.06	5.16±1.18	1/1
	4.19±1.09	4.44±1.05	
HDL (mmol/l) M1/M12	1.50±0.43	1.55±0.41	1/0.83
	1.16±0.37	1.38±0.55	
LDL (mmol/l) M1/M12	2.58±0.87	2.92±0.92	1/1
	2.25±0.90	2.39±0.68	
TAG (mmol/l) M1/M12	1.57±0.73	1.52±0.51	1/1
	1.76±0.93	1.73±1.40	
HbA1C (mmol/mol) M1/M12	39.7±7.8	40.9±7.8	1/1
	46.5±17.4	46.2±15.9	
ACE-inhibitors (%) M1/M12	25.9	2.9	0.60/1
	29.6	17.1	
Dihydropyridine calcium channel blockers (%) M1/M12	23.5	25.7	1/1
	38.3	22.9	
ACE-inhibitors + Dihydropyridine calcium channel blockers (%) M1/M12	8.6	0	1/1
	16.1	8.6	
Heart rate mean M1/M12	79 ± 9	81 ± 7	1/1

	Non-progression (70 %) n=81	Progression (30 %) n=35	P-value (after Bonferroni correction)
	84 ± 9	82 ± 8	

BMI – body mass index; CMV – cytomegalovirus; HbA1C – glycated haemoglobin; HTx – heart transplant;

ICMP – ischaemic cardiomyopathy; M – month; TAG – triacylglycerols; VAD – ventricular assist device.

* according to ISHLT classification (3A)

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Table 4

Predictive factors of CAV progression, with the patient cohort divided into quartiles based on IT progression 12 mo after HTx

	M1 after HTx	M12 after HTx	Change (M12-M1)	P-value (after Bonferroni correction)
HR min	68±9	68±8	-1±9	1
HR max	103±16	113±16	9±21	<0.001
HR mean	80±8	83±8	2.5±9.9	0.06
APC/hour	1.9 (0.7~3.9)	0.3 (0.1~0.9)	-1.1 (-2.5~-0.2)	<0.001
VPC/hour	0.5 (0.2~1.3)	0.1 (0.0~0.5)	-0.2 (-0.8~0.08)	0.181

APC – atrial premature complex; VPC – ventricular premature complex; HTx – heart transplant; M – month

Table 5

Correlation between intimal thickness progression and individual 24- hour ECG Holter variables at M1 and M12

	M1 after HTx	M12 after HTx
HR min	R=-0.00, p=0.99	R=-0.15, p=0.13
HR max	R=0.16, p=0.10	R=-0.02, p=0.84
HR mean	R=0.02, p=0.83	R=-0.13, p=0.18
APC/hour	R=0.18, p=0.053	R=-0.03, p=0.79
VPC/hour	R=0.06, p=0.54	R=-0.12, p=0.23

APC – atrial premature complex; ECG – electrocardiogram; HR – heart rate; HTx – heart transplant; IT – intimal thickness; M – month; VPC – ventricular premature complex

Table 6

Associations between intimal thickness progression (IT) and HR-slowing medication at M1 and M12

	M1 after HTx		M12 after HTx	
	Treatment=YES	Treatment=NO	Treatment=YES	Treatment=NO
Beta blockers	21.8±25.1 (n=60)	25.6±35.2 (n=56)	21.3±28.3 (n=77)	27.9±34.1 (n=39)
P	0.50		0.32	
Dose of beta blockers (mg) vs. IT	R=−0.04, p=0.687		R=−0.20, p=0.035	
Ivabradine	24.3±27.3 (n=2)	23.6±30.5 (n=114)	34.5±35.7 (n=16)	21.9±29.2 (n=100)
P	0.98		0.19	
Dose of ivabradine (mg) vs. IT	R=0.02, p=0.826		R=0.17, p=0.069	
Bradycardic medication (beta blocker, ivabradine, beta blocker + ivabradine)	22.1±25.1 (n=61)	25.3±35.4 (n=55)	24.3±30.8 (n=86)	21.8±29.4 (n=30)
p	0.58		0.70	

Numbers are IT in micrometres

HTx- heart transplant; M- month; mg- milligram