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Received: 15 April 2021 | Revised: 30 August 2021 | Accepted: 8 September 2021

DOI: 10.1111/ctr.14488

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research
WILEY

ORIGINAL ARTICLE

A randomized clinical study using optical coherence tomography to evaluate the short-term effects of high-intensity interval training on cardiac allograft vasculopathy: a HITTS substudy

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Funding information
EkstraStiftelsen Helse og Rehabilitering (Stiftelsen Dam), Grant/Award Number: 2018/FO189552; Fredriksens Fond

Abstract

Cardiac allograft vasculopathy (CAV) remains a leading cause of long-term mortality after heart transplantation. Both preventive measures and treatment options are limited. This study aimed to evaluate the short-term effects of high-intensity interval training (HIT) on CAV in de novo heart transplant (HTx) recipients as assessed by optical coherence tomography (OCT). The study population was a subgroup of the 81-patient HITTS study in which HTx recipients were randomized to HIT or moderate intensity continuous training (MICT) for nine consecutive months. OCT images from baseline and 12 months were compared to assess CAV progression. The primary endpoint was defined as the change in the mean intima area. Paired OCT data were available for 56 patients (n = 23 in the HIT group and n = 33 in the MICT group). The intima area in the entire study population increased by 25% [from 1.8±1.4 mm^2 to 2.3±2.0 mm^2, $P < .05$]. The change was twofold higher in the MICT group (.6±1.2 mm^2) than in the HIT group (.3±.6 mm^2). However, the treatment effect of HIT was not significant (treatment effect = −.3 mm^2, 95% CI [−.825 to .2 mm^2] $P = .29$). These results suggest that early initiation of HIT compared with MICT does not attenuate CAV progression in de novo HTx recipients.

KEYWORDS
clinical trial, rehabilitation, vasculopathy

1 | INTRODUCTION

Cardiac allograft vasculopathy (CAV) is one of the leading causes of late mortality after heart transplantation.[1] It is an accelerated form of coronary artery disease (CAD) characterized by diffuse and concentric intimal proliferation of the epicardial and intramyocardial arteries, unlike focal lesions usually seen in native coronary artery disease.[2] The pathomechanism of CAV is multifactorial, and a commonly accepted theory is that CAV is caused by repeated immunological (e.g., acute rejection and anti-HLA antibodies) and non-immunological (e.g., hypertension, hyperlipidemia, and insulin resistance) insults.[3] These insults cause endothelial cell damage and trigger a cascade of immune responses that lead to vascular remodeling, luminal narrowing, and eventually impaired blood flow.[4] Since treatment options for CAV are limited, the

main focus has been attributed to prophylaxis, which may be achieved by treating various risk factors.

Accumulating data implies that attenuation of CAV may be possible with exercise through modification of non-immunological pathways. An intravascular ultrasound (IVUS) study has previously shown that high-intensity interval training (HIT) results in attenuation of CAV progression in maintenance heart transplant (HTx) recipients.[5] Several other studies have shown greater efficacy of HIT compared to moderate intensity continuous training (MICT) on CAD risk factors and peak oxygen consumption ($VO_{2\,peak}$) in various populations, including those with established cardiovascular disease and in maintenance HTx recipients.[6–11] HIT was also superior to MICT in improving $VO_{2\,peak}$ in the HITTS study (High-Intensity Interval Training in De Novo Heart Transplant Recipients in Scandinavia).[12] However, the effects of HIT on CAV in de novo HTx recipients have not been investigated.

Coronary angiography is the current standard for screening CAV.[13] An angiogram fills the vessel lumen with contrast but does not provide visual information about the arterial wall, and early CAV may be hard to detect. Both IVUS and optical coherence tomography (OCT) are imaging modalities with improved sensitivity that enables detection and evaluation of sub-angiographical CAV. However, OCT produces images with 10 times the spatial resolution of IVUS, providing a clear delineation of the arterial vessel and in-vivo vessel histological analysis.[14,15] In addition, compared to IVUS and coronary angiography, OCT has a superior interobserver correlation.[16] With the given limitations of coronary angiography and current protocols in preventing CAV, this HITTS substudy was designed to utilize the advantages of OCT to evaluate the effects of HIT on CAV in de novo HTx recipients.

2 | MATERIAL AND METHODS

This study was approved by the South-East Regional Committee for Medical and Health Research Ethics in Norway (ref no: 2012/2305) and registered at ClinicalTrials.gov (NCT01796379). The study was conducted in compliance with Good Clinical Practice, the requirements of the local ethics review board, and the tenets of the Declaration of Helsinki.

2.1 | Patient population

The study population was a subgroup of the 81-patient HITTS study; a multicenter randomized controlled trial described previously.[17] The main inclusion criteria in the HITTS study were as follows: (1) clinically stable de novo HTx recipients at 6–8 weeks after heart transplantation, (2) age > 18 years, (3) either sex, (4) receiving immunosuppressive therapy according to local protocols, (5) willing and able to give written informed consent for study participation, and (6) motivated to participate in the study for 9 months. The application of these inclusion criteria resulted in 81 de novo HTx recipients being randomized at a 1:1 ratio to nine consecutive months of HIT or MICT. The participants were given similar lifestyle advice on diet, daily physical activity and smoking cessation. Local physical therapists supervised the intervention exercise. HIT consisted of 4 × 4-min intervals at 85–95% of the peak effort with 3 min of active recovery at 60–70% of the peak effort between intervals. MICT, which is equivalent to standard exercise-based cardiac rehabilitation in HTx recipients recommended by the European Society of Cardiology, consisted of 25 min of continuous training at 60–80% of the peak effort.[18] Both groups performed supplementary strength training. Each patient completed approximately 58 training sessions during the intervention period. Only patients at Oslo University Hospital, Rikshospitalet, Oslo, Norway, who had OCT recordings performed were included in this HITTS substudy.

2.2 | Outcomes

The primary endpoint was defined as the change in the mean intima area from baseline to 12 months. The secondary endpoints were as follows: (1) the change in the mean lumen area; (2) the changes in the plaque burden, macrophages, and thrombus; (3) the change in the maximum intima thickness (MIT); and (4) the change in the intima-media ratio (IMR).

2.3 | Optical coherence tomography

OCT images were acquired in the left anterior descending artery using the C7 Dragonfly device (St Jude Medical, St Paul, MN, USA) during 2013 and 2014, and the Dragonfly Duo device (St Jude Medical) from 2015 onwards. OCT recordings were acquired at a motorized pullback speed of 20 mm/s and a frame rate of 100/s while injecting contrast at 4 ml/s (total of 14–18 ml). The maximum pullback length was 75 mm.

Post-hoc image analysis was conducted offline and in accordance with consensus recommendations at a laboratory blinded to the interventional status (Oslo University Hospital, Rikshospitalet, Oslo, Norway in collaboration with Aarhus University Hospital, Aarhus, Denmark), using a customized version of QCU-CMS software (Leiden University Medical Center, The Netherlands).[19] Lumen, intima, and media areas were obtained on cross-sectional frames that were precisely matched between baseline and 12 months by contouring the lumen and trilaminar vessel wall with a 1-mm longitudinal sampling frequency (approximately every fifth frame) (Figure 1). The vessel wall was not analyzed in frames with side branches and atherosclerotic plaques if the external elastic membrane was obscured. The mean intima area was defined as the sum of the measured intima areas divided by the number of frames in which the intima-media interface was analyzed. IMR was defined as the mean intima area divided by the mean media area. The distribution of plaques and macrophages was determined by delineating lateral plaque borders, measuring the angulation, and reporting it as a percentage of the total circumference in the analyzed frames.

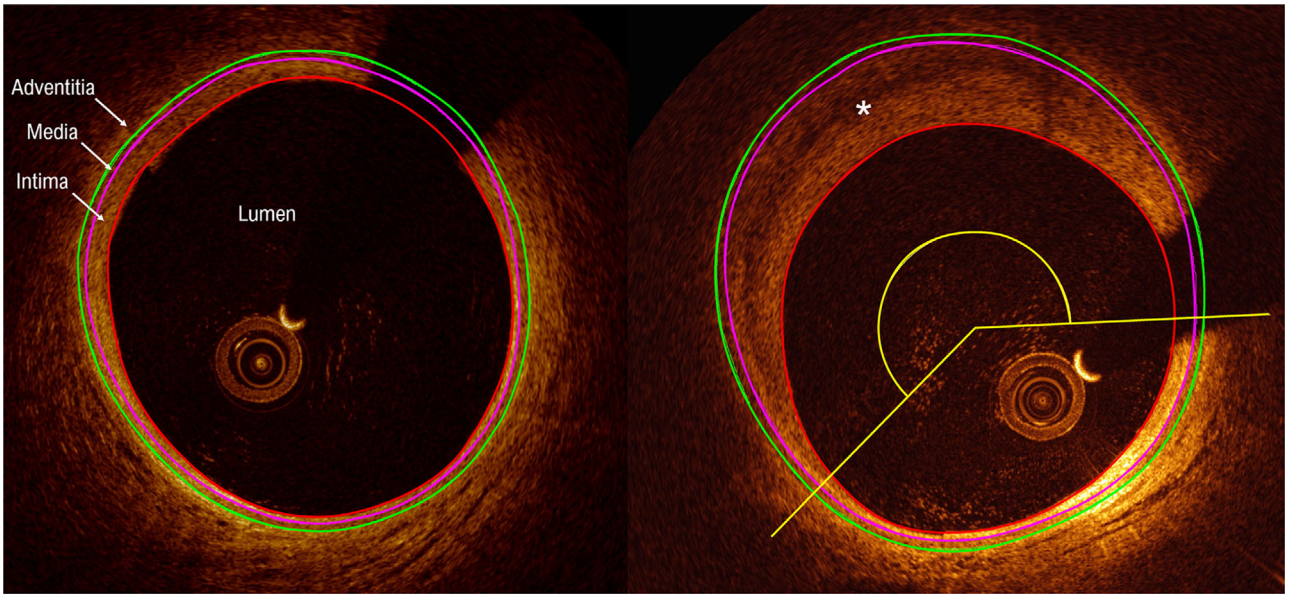

FIGURE 1 Matched optical coherence tomography (OCT) images. Left image, normal vessel at baseline; right image, fibrotic plaque at 12-month; red circle, luminal border; pink circle, intima-media interface; green circle, media-adventitia interface; asterisk, plaque; yellow arc, plaque angle

2.4 | CAV grading

CAV grading was performed according to the nomenclature recommended by the International Society for Heart and Lung Transplantation for CAV.[20] Left ventricular ejection fraction (LVEF), restrictive physiology, and coronary artery stenosis were assessed by routine echocardiography, right heart catheterization, and coronary angiography, respectively. LVEF was mainly quantified using Simpson's rule. The right atrial pressure and pulmonary capillary wedge pressure were determined by direct measurements, while the cardiac output was obtained by thermodilution. Coronary angiography was performed in all HTx recipients as a part of a routine diagnostic workup. At least two projections were obtained of all major coronary arteries with almost identical angulations at baseline and 12 months. Any primary vessel or major secondary branch with visual stenosis of > 30% was reassessed offline using two-dimensional quantitative coronary angiography (2D-QCA; QAngioXA 7.3, Medis Medical Imaging, The Netherlands).

2.5 | Rejection score

The presence of cellular rejection was based on the revised version of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection as follows: grade 1 R, mild rejection; grade 2 R, moderate rejection; and grade 3 R, severe rejection.[21] The rejection score was calculated as (number of grade 1 R rejections) x1 + (number of grade 2 R rejections) x2 + (number of grade 3 R rejections) x3.

2.6 | Statistical methods

Histograms, Q-Q plots, and the Shapiro–Wilk test were used to check whether continuous values conformed to a normal distribution; those that did are presented as mean ± standard-deviation values, while non-normally distributed data are presented as median and interquartile range [IQR] values. Categorical data are presented as absolute values with percentages. Continuous baseline data were compared between groups using the t-test or Mann-Whitney U tests, as appropriate. Categorical variables were analyzed using the chi-square test or Fisher's exact test, as appropriate. Comparisons within and between groups of variables with repeated measurements were performed using mixed-model analysis of variance. The threshold for statistical significance was set at $P < .05$, and all tests were two-sided. All analyses were performed using Stata SE 16 (StataCorp, College Station, TX, USA).

3 | RESULTS

3.1 | Patient population

This study assessed the suitability of 89 de novo HTx recipients for inclusion during the enrollment period (Figure 2). Sixty-eight patients were eligible, and they were randomized after obtaining informed written consent into the HIT group ($n = 32$) or the MICT group ($n = 36$). As illustrated in Figure 2, OCT was not performed at baseline or 12 months in 11 patients for various reasons ($n = 9$ in the HIT group and $n = 2$ in the MICT group), and the data were not matchable for one patient in the MICT group. None of the patients were excluded due to HTx-related complications, and all of the randomized patients were

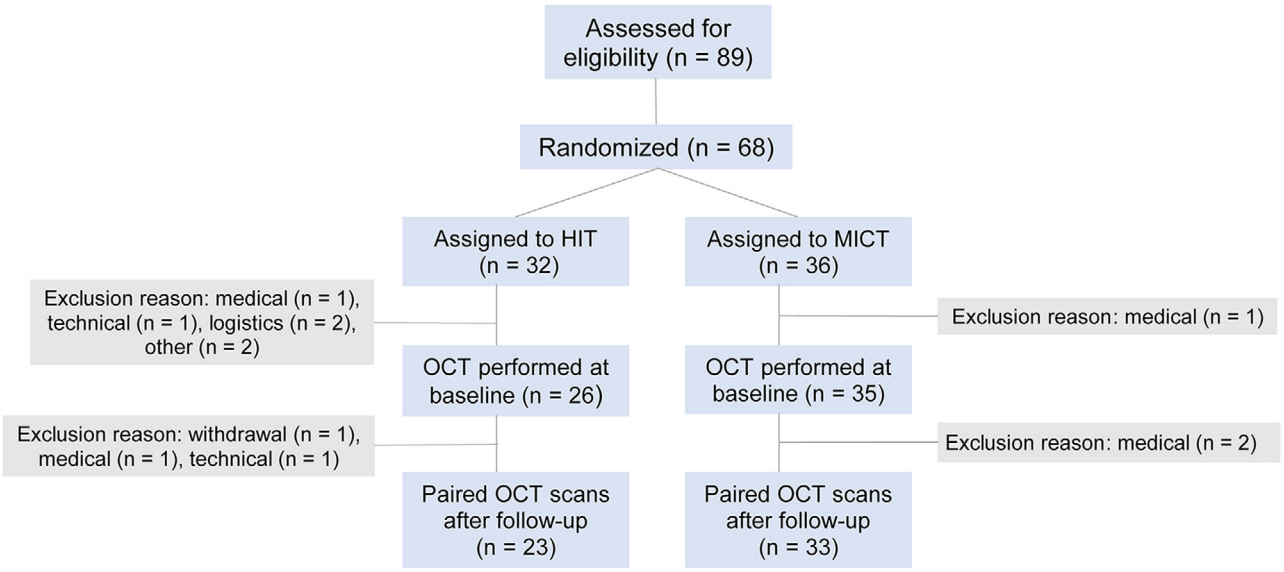

FIGURE 2 Selection, enrollment, and reason for exclusion of study patients. HIT, high-intensity interval training; MICT, moderate-intensity continuous training; OCT, optical coherence tomography

alive at 12 months after heart transplantation. There were no serious adverse events related to any of the procedures. Matched OCT data were available for 56 recipients ($n = 23$ in the HIT group and $n = 33$ in the MICT group) at 12 months, and they were included in the analysis.

3.2 | Baseline characteristics

Baseline characteristics were similar in the HIT and the MICT groups (Table 1). The overall age was 33 [26–48] years for donors and 52 [41–56] years for recipients. Most of the included recipients were male (77%). The cold ischemic time was 212 [103–243] min, and cytomegalovirus mismatch was evident in 38% of the patients. The leading reason for heart transplantation was dilated cardiomyopathy (38%). Both groups received similar medications at baseline, with the combination of cyclosporine with mycophenolate being the most frequently applied immunosuppressive therapy (Table 2). Early initiation of everolimus was preferred for patients with vulnerable renal function before HTx and those who developed calcineurin inhibitor-induced renal failure after HTx. The dosage of corticosteroids was tapered gradually and administered to all patients throughout the study period. Antiplatelet treatment and anticoagulation were not initiated as standard therapy, whereas a statin was administered to all patients before baseline testing.

3.3 | Optical coherence tomography

The number of paired cross-sectional slices that were examined for each patient was 52±15. The mean intima area in the entire study population increased by 25%, from 1.8±1.4 mm^2 to 2.3±2.0 mm^2 (change = .5±1.0 mm^2, $P < .05$). The change in the mean intima area was twofold higher in the MICT group than in the HIT group (Table 3 and Figure 3). Despite this, the treatment effect of HIT was not significant (Table 3). The mean lumen area in the entire study population decreased by 5%, from 11.8±3.2 mm^2 to 11.2±3.2 mm^2 (change = –.6±1.1 mm^2, $P < .05$). The change in the mean lumen area was significant and similar within both groups (Table 3 and Figure 4). In the entire study population, MIT increased from .45±.26 mm to .54±.32 mm (change = .09±.15 mm, $P < .05$) and IMR from 1.3±.5 to 1.6±.9 (change = .4±.6, $P < .05$). The changes in MIT and IMR were also significant within both groups. A rapid change in MIT, defined as an increase ≥.5 mm from baseline to 12 months, was evident for one patient in the HIT group ($n = 1$) and one patient in the MICT group ($n = 1$). However, there were no significant differences between the groups for any of the changes mentioned above (Table 3), and there was no obvious intervention effect in multivariate analysis when adjusted for known risk factors (Table 4).

The qualitative vessel analysis revealed an abnormal vessel type (i.e., a plaque, macrophage, or thrombus) in 65% of the overall population at baseline and 70% at 12 months. In addition, the prevalence of the fibrotic phenotype, which was the most common abnormal finding in the entire study population, increased from 11±16% of the total circumference to 17±22% ($P < .05$), while changes in the distribution of lipids, calcium, macrophages and thrombus were not significant (data not shown). However, the treatment effect of HIT was not significant for any of the analyzed qualitative OCT variables (Table 3).

3.4 | Coronary angiography and 2D-QCA

CAV was apparent in 10 patients at baseline ($n = 4$ in the HIT group and $n = 6$ in the MICT group) and 20 patients at follow-up ($n = 8$ in the HIT and 12 in the MICT group). Most of these patients had subtle changes. Only one patient at baseline ($n = 1$ in the MICT group) and four patients at follow-up ($n = 1$ in the HIT group and $n = 3$ in the MICT group) were diagnosed with coronary artery stenosis of > 30%. These

TABLE 1 Patient characteristics and medications at baseline

	HIT group ($n = 23$)	MICT group ($n = 33$)	*P*
Characteristics			
Age of recipient (years)	47 [40 to 56]	54 [42 to 57]	.53
Age of donor (years)	32 [22 to 49]	33 [29 to 48]	.58
Sex of recipient (male)	17 (74)	26 (79)	.67
Sex of donor (male)	17 (74)	24 (73)	.92
LVAD	3 (13)	4 (12)	1.00
Ischemic time (min)	205 [134 to 230]	214 [96 to 248]	.64
Recipient positive for CMV	16 (70)	18 (55)	.26
Donor positive for CMV	14 (64)	26 (79)	.22
Body-mass index (kg/m^2)	24±3	25±4	.29
Former smoker	10 (43)	15 (47)	.80
Reason for transplantation			.35
DCM	8 (35)	13 (39)	
ICM	8 (35)	6 (18)	
Other	7 (30)	14 (42)	
Immunosuppressant			
Cyclosporine	16 (70)	28 (85)	.20
Tacrolimus	6 (26)	5 (15)	.33
Everolimus	10 (43)	10 (30)	.31
Mycophenolate	20 (87)	30 (91)	.64
Prednisolone	23 (100)	33 (100)	1.00
Medication at baseline			
Antiplatelet agents	3 (13)	3 (9)	.68
Anticoagulation	2 (9)	1 (3)	.56
Beta-blockers	6 (26)	9 (27)	.92
ACE inhibitors	0 (0)	1 (3)	1.00
Angiotensin-receptor blockers	2 (9)	1 (3)	.56
Statins	22 (96)	32 (97)	1.00
Diuretics	20 (87)	30 (91)	.68
Diabetes medication and insulin therapy	3 (13)	1 (3)	.30

Data are n (%), median [IQR], or mean±SD values.
P values are for between-groups comparisons at baseline.
Abbreviations: IQR, interquartile range; SD, standard deviation; LVAD, left ventricular assist device; CMV, cytomegalovirus; DCM, dilated cardiomyopathy; ICM, ischemic cardiomyopathy; ACE, angiotensin-converting enzyme; HIT, high-intensity interval training; MICT, moderate intensity continuous training.

vessels were analyzed offline using 2D-QCA. The results showed that the mean grade of stenosis did not increase compared with the initial assessment and that the mean grade of stenosis did not differ significantly between groups at baseline and 12 months (Table 3).

3.5 | Exploratory variables

The exploratory variables did not differ significantly between the HIT and MICT groups (Table 2). However, several variables changed significantly for the entire study population and within the groups. The systolic blood pressure (BP) increased significantly for the entire study population (from 132±12 to 136±14 mm Hg, change = 4±13 mm Hg, $P < .05$) and in the HIT group, as did the diastolic BP for the entire study population (81±7 mm Hg to 84±8 mm Hg, change: 3±8 mm Hg, $P < 0,05$) and the HIT group. Neither the systolic BP nor the diastolic BP changed significantly in the MICT group.

Blood tests in the entire study population revealed significant reductions in the levels of serum creatinine (from 121±53 to

TABLE 2 Exploratory variables

	HIT group $n = 23$		MICT group $n = 33$		HIT group $n = 23$	MICT group $n = 33$	Treatment effect	
	Baseline	12 months	Baseline	12 months	Change from baseline to 12 months		Change (95% CI)	*P*
Biochemistry								
CRP (mg/L)	2.7 [.6 to 5.7]	1.8 [.6 to 5.5]	2.0 [.7 to 6.7]	2.4 [.7 to 3.9]	−.6 [−3.1 to .6]	.05 [−3.6 to 1.3]	5 (−2 to 13)	.17
HbA1c (%)	5.5 [5.2 to 6.5]	5.5 [5.1 to 6.8]	5.5 [5.1 to 6.1]	5.6 [5.2 to 5.9]	.1 [−.7 to .2]	−.1 [−.3 to .3]	.2 (−.1 to .7)	.19
Total cholesterol (mmol/L)	5.2 [4.5 to 6.2]	5.1 [4.7 to 5.6]	4.9 [4.4 to 6]	4.5 [3.8 to 6.1]	−.2 [−1 to .6]	−.2 [−.7 to .4]	−.2 (−.9 to .5)	.66
LDL cholesterol (mmol/L)	3 [2.2 to 3.8]	2.9 [2.5 to 3.2]	2.6 [2.1 to 3.1]	2.4 [2 to 3.3]	.1 [−.7 to .5]	−0,2 [−.4 to .4]	−.2 (−.7 to .4)	.60
HS-troponin T (ng/L)	30 [19 to 67]	13 [8 to 23]	32 [20 to 54]	13 [10 to 27]	−17 [−37 to −5]	−17 [−26 to −8]	−3 (−20 to 14)	.72
NT-proBNP (pmol/L)	98 [64 to 217]	40 [13 to 61]	111 [74 to 179]	29 [21 to 58]	−51 [−173 to −37]	−69 [−121 to −19]	−50 (−117 to 18)	.15
Creatinine (μmol/L)	115±21	98±20	123±27	106±26	−19±22	−17±25	−2 (−14 to 10)	.77
eGFR, < 60 ml/min	12 (52)	5 (22)	17(53)	13 (41)	13 (41)	13 (41)		.20
Blood pressure (mm Hg)								
Systolic	130±10	137±10	133±14	136±16	7±10	2±15	5 (−2 to 12)	.18
Diastolic	79±6	85±6	81±8	83±10	6±6	2±9	4 (−.01 to 8)	.05
Peak oxygen consumption								
Vo2peak, L/min	1.54±.44	2.10±.62	1.64±.44	2.01±.61	.5±.4	.3±.4	.2 (.01 to .4)	<.05
Rejection score								.37
0	16 (70)	16 (70)	20 (61)	16 (48)				
1	4 (17)	3 (13)	6 (18)	7 (21)				
2	1 (4)	1 (4)	3 (9)	6 (18)				
3	1 (4)	2 (9)	2 (6)	1 (3)				
4	0	0	0	0				
5	1 (4)	0	2 (6)	3 (9)				
6	0	1 (4)	0	0				
CAV grade								.97
0	18 (78)	16 (70)	27 (82)	21 (64)				
1	5 (22)	5 (22)	6 (18)	11 (33)				
2	0	1 (4)	0	1 (3)				
3	0	1(4)	0	0				

Data are *n* (%), median [IQR], mean±SD values or mean (95% CI).

P values are from mixed-effects multilevel regression and are for between-groups comparisons.

Abbreviations: IQR, interquartile range; SD, standard deviation; CI, confidence interval; HbA1c, glycated hemoglobin; LDL, low-density lipoprotein; HS, high-sensitivity; NT-proBNP, N-terminal pro-brain natriuretic peptide; CAV, cardiac allograft vasculopathy; eGFR, estimated glomerular filtration rate; Vo2peak, peak oxygen consumption; HIT, high-intensity interval training; MICT, moderate intensity continuous training.

103±24 μmol/L, change = −17±23 μmol/L, $P < .05$), high-sensitivity troponin T (from 32 ng/L [−20 to 61 ng/L] to 13 ng/L [9 to 24 ng/L], change = −17 ng/L [−8 to −26 ng/L], $P < .05$) and NT-proBNP (N-terminal pro-brain natriuretic peptide) (from 107 pmol/L [74 to 189 pmol/L] to 35 pmol/L [19 to 60 pmol/L], change = −62 pmol/L [−35 to −123 pmol/L], $P < .05$). These changes were also significant in both groups (data not shown). The rejection score change was not significant for the entire study population and the HIT group, while it increased significantly in the MICT group (data not shown). However, there were no significant differences between the groups for any of the variables. Although the usage of everolimus in the entire study population increased from 36% at baseline to 45% at follow-up, the statistical difference between groups remained insignificant.

4 | DISCUSSION

The main finding of this randomized study evaluating the short-term effects of HIT in de novo HTx recipients is that HIT, despite favorable numerical effect, did not significantly reduce CAV progression the first year after HTx, as assessed by OCT. We found that CAV develops early

TABLE 3 CAV assessment

	HIT group $n = 23$		MICT group $n = 33$		HIT group $n = 23$	MICT group $n = 33$		
	Baseline	12 months	Baseline	12 months	Change from baseline to 12 months		Treatment effect Change (95% CI)	*P*
OCT (quantitative)								
Intima area (mean), mm^2	1.7±1.2	2.0±1.5	1.9±1.5	2.5±2.3	.3±.6	.6±1.2	−.3 (−.8 to .2)	.29
Intima area (minimum), mm^2	.9±.8	1.0±1.2	.9±.7	1.2±1.3	.1±.5	.3±.9	−.2 (−.6 to .2)	.35
Intima area (maximum), mm^2	3.1±1.9	3.9±2.6	3.4±2.1	4.3±3.2	.8±1.1	1.0±1.7	−.2 (−1.0 to .5)	.56
Lumen area (mean), mm^2	11.4±2.7	10.9±2.8	12.1±3.5	11.5±3.4	−.6±1.2	−.6±1.0	−.01 (−.6 to .5)	.97
Lumen area (minimum), mm^2	7.1±2.4	6.7±2.5	7.1±3.4	7.2±3.2	−.4±1.8	.1±1.5	−.5 (−1.4 to .3)	.26
Lumen area (maximum), mm^2	16.9±5.0	16.3±5.0	18.2±5.0	17.0±5.0	−.6±2.0	−1.2±2.0	.6 (−.4 to 1.7)	.26
Maximum intima thickness, mm	.4±.3	.5±.4	.5±.3	.6±.3	.1±.2	.1±.2	−.07 (−.08 to .1)	.86
Intima-media ratio	1.3±.5	1.6±.9	1.3±.4	1.7±.9	.3±.6	.4±.6	−.1 (−.4 to .2)	.60
OCT (qualitative), % of total circumference								
Fibrous plaques	11.2±18.0	16.2±24.6	11.2±14.7	17.2±20.7	5.0±12.5	6.0±12.9	−1.0 (−7.7 to 5.6)	.76
Lipid plaques	.8±1.9	.9±2.1	.8±2.5	.8±2.6	.1±.4	.03±.2	.1 (−.05 to .3)	.19
Calcium plaques	.5±1.8	.6±2.0	.2±.8	.2±.8	.05±.2	−.001±.06	.1 (−.01 to .1)	.11
Macrophages	.2±.6	.1±.5	.1±.3	.1±.2	−.1±.3	−.02±.2	−.1 (−.2 to .1)	.23
Thrombus	.004±.019	.009±.041	.021±.121	.035±.203	.005±.046	.01±.08	−.01 (−.05 to .03)	.61
2D-QCA, % stenosis								
	3±8	5±10	3±9	9±13	2±7	6±10	−4 (−8.6 to .5)	.08

Data are mean±SD or mean (95% CI) values.
Changes between baseline and 12 months and the treatment effect were calculated for patients for whom data from both time points were available.
P values for the treatment effect are from mixed-effects multilevel regression.
Abbreviations: SD, standard deviation; CI, confidence interval; OCT, optical coherence tomography; 2D-QCA, two-dimensional quantitative coronary analysis; HIT, high-intensity interval training; MICT, moderate intensity continuous training.

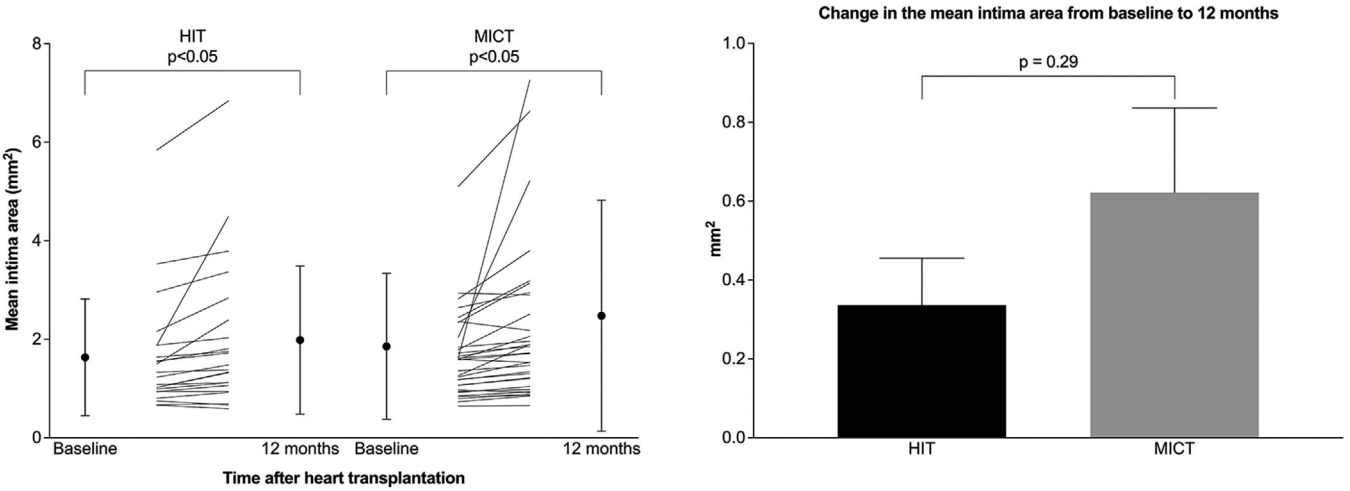

FIGURE 3 Mean intima area at baseline and 12 months after heart transplantation. Solid circles indicate means, bars in left panel indicate standard deviations (SDs), thin lines indicate changes between baseline and the 12-month for individual patients, and T-bars in right panel indicate standard errors

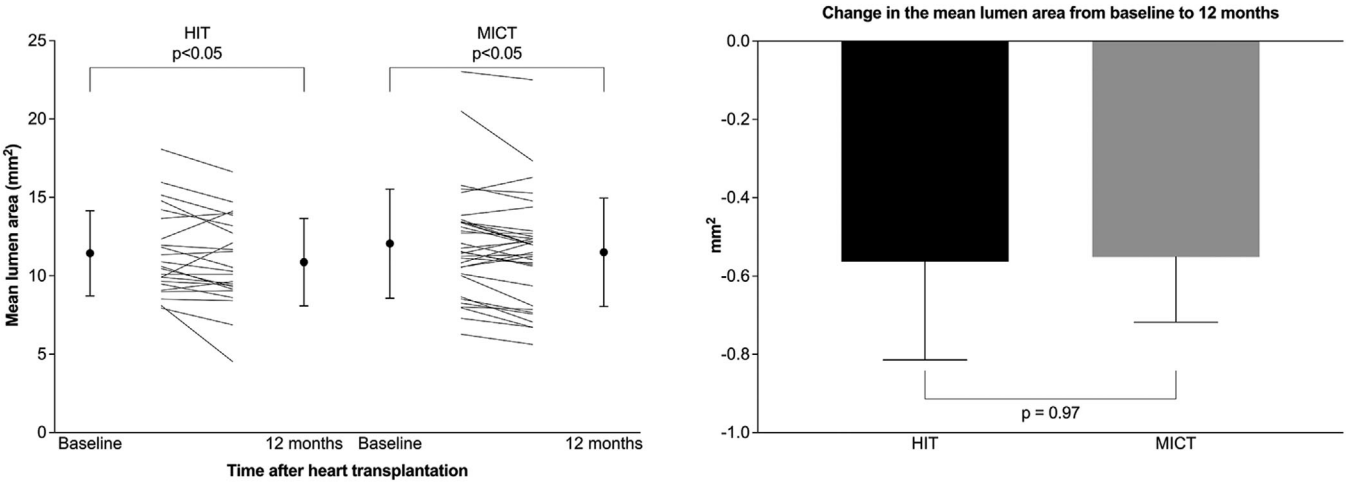

FIGURE 4 Mean lumen area at baseline and 12 months after heart transplantation. Solid circles indicate means, bars in left panel indicate SDs, thin lines indicate changes between baseline and the 12-month for individual patients, and T-bars in right panel indicate standard errors

TABLE 4 Uni- and multivariate linear regression analysis for change in the mean intima area

Covariate	Univariate	*P*	Multivariate	*P*
Sex of recipient	.02 (−.63 to .67)	.95	.28 (−.44 to .99)	.44
Age of recipient	.01 (−.01 to .03)	.20	.01 (−.01 to .04)	.23
Former smoker	.48 (−.07 to 1.02)	.09	.43 (−.15 to 1.01)	.15
Diabetes	.08 (−1.00 to 1.15)	.89	−.07 (−1.18 to 1.04)	.89
Use of everolimus	−.22 (−.77 to .33)	.42	−.29 (−.87 to .29)	.32
HIT	−.29 (−.84 to .27)	.31	−.24 (−.82 to .34)	.34

Data are beta coefficients with 95% CI.
Abbreviations: CI, confidence interval; HIT, high-intensity interval training.

after heart transplantation and that the mean intima area increased by 25% within the first year. We also confirmed the limitations of using coronary angiography to detect early CAV.

Annual coronary angiography is the current method recommended for the screening and surveillance of CAV, although it has low sensitivity compared with intracoronary imaging modalities. IVUS detects CAV in approximately 50% of patients without angiographic CAV.[22] The present study found that 36% of the patients had angiographic CAV at 12 months after heart transplantation, while approximately 70% were diagnosed with abnormal vessel-wall structure as assessed by OCT at the same time point, thereby confirming the limitations of coronary angiography in detecting and evaluating early CAV. This discrepancy can be attributed to the concentric and longitudinal distribution of CAV, and the outward remodeling of the coronary artery vessel wall, also evident in the current study in which the mean intima area increased by 25%. In comparison, the lumen area only decreased by 5%.

So why did the significant improvement in $VO_{2\,peak}$ with HIT compared with MICT in the HITTS study fail to show any beneficial effects on CAV? Several studies have demonstrated the superiority of HIT over MICT in improving $VO_{2\,peak}$ in different patient populations, including maintenance HTx recipients.[9–11,23] Nytrøen et al. found that HIT also had beneficial effects on CAV as assessed by IVUS.[5] HIT may positively affect CAV via mediating reduction in cardiometabolic risk factors.[6–8] This seems particularly relevant, given that 95% of HTx recipients develop systemic arterial hypertension, 81% develop hyperlipidemia, 33% develop renal failure, and 32% develop type 2 diabetes mellitus.[24] However, a recent meta-analysis of the effects of HIT in a wide array of patient populations, including HTx recipients, did not support a generally beneficial effect on cardiometabolic risk factors.[25] HIT has been found to improve $VO_{2\,peak}$ in normal-weight and overweight/obese populations, but improvements in metabolic risk factors (BP, diabetes, and body fat composition) have only been demonstrated in overweight/obese patients. Consistent with this, we found no improvements in metabolic risk factors in our study population with a mean body mass index (BMI) of 24.5 kg/m^2 at baseline. Indeed, diastolic BP, BMI, and body fat increased significantly more in the HIT group than in the MICT group in the main HITTS study.[12]

Statins appear to reduce inflammation by lowering lipid levels and may also mediate anti-inflammatory activity and cytokine suppression, resulting in a decreased incidence of CAV.[26] This suggests that HTx recipients also experience significant immune-mediated involvement of the graft vasculature. In addition, elevated levels of C-reactive protein (CRP) are associated with the development of CAV.[27] Previous studies have demonstrated that exercise mediates an

anti-inflammatory effect and a reduction in CRP.[9] However, we did not find any beneficial effect of HIT over MICT for any of the measured biomarkers, including CRP.

Nytrøen et al. found that 12 months of HIT compared with no structural intervention results in improved $VO_{2\ peak}$ and attenuation of CAV progression in maintenance HTx recipients.[5,11] In the HITTS study, 12 months of HIT compared with MICT in de novo HTx recipients also resolved in improved $VO_{2\ peak}$.[12] The significant change in $VO_{2\ peak}$ was similarly evident in the subpopulation of the current study, indicating that there was no selection bias. The magnitude of $VO_{2\ peak}$ change in the treatment groups of the HITTS study was higher than in other studies conducted in maintenance HTx recipients, and the differences could not account for the diminished observed effects.[28] However, the current substudy did not find significant benefits of HIT over MICT for any of the measured OCT outcomes, including the mean intima area. Exercise duration is an effect modifier for functional capacity in HTx recipients.[29] Hence, a mismatch in the exercise duration (9 vs. 12 months) may have caused the discrepancy between the current study results and a previous study in which HIT marginally attenuated CAV progression.[5] Nevertheless, the beneficial effect of HIT over MICT on CAV does not seem to be evident if it is initiated early. Hence, it can be hypothesized that the effect of HIT is time-dependent.

The mean intima area increased significantly in both groups by 25%. This is consistent with previous IVUS and OCT studies in which a profound increase in the intima thickness was found during the first year after heart transplantation.[15,22,30] Furthermore, the increase in the mean intima area was mainly mediated by increased fibrous tissue distribution, while regular atherosclerotic plaques remained unchanged. This result is also highly consistent with previous findings by Clemmensen et al.[15] and supports the idea that layered fibrotic plaque may be the main component involved in the early CAV progression.

This randomized study has some important limitations. The statistical power analysis was performed for the outcomes in the main HITTS and not the current substudy. The sample size was small and probably insufficient to detect a statistically significant effect on CAV in the HIT group. A type 2 error can be suspected, particularly for the primary endpoint since the numerical change was twofold higher in the MICT group. The follow-up period was short, and a long-term follow-up may have presented different results. However, preliminary results of angiographic CAV at 3 years for available patients ($n = 22$ in the HIT group and $n = 30$ in the MICT group) showed no significant difference in CAV grade between the groups (data not shown). It is also impossible to exclude that patient-related interventions such as differences between groups in self-initiated exercise and dietary habits may have affected the outcomes. Furthermore, even if a rapid increase in MIT detected with IVUS is an established negative prognostic factor in HTx recipients, the importance of intracoronary imaging for detection of early CAV has recently been questioned.[22,31]

ACKNOWLEDGMENTS

This study was supported by Stiftelsen DAM [2018/FO189552] and Fredriksens Fond. We thank the staff at the Department of Cardiology, Oslo University Hospital, Rikshospitalet for assistance during OCT acquisition, right heart catheterization and echocardiography; we thank study nurse Bjørklund for coordinating the OCT procedures; we thank Dr. Lie for valuable discussions on performing statistical analysis and interpretation of the results, and we thank Dr. Ahmad for critical reading of the manuscript.

CONFLICT OF INTEREST

M.R. received institutional research grants from Stiftelsen DAM and Fredriksens Fond; L.G. received personal fees from Astra Zeneca, Boehringer Ingelheim, Novartis, and Amgen during the conduct of the study; N.R.H. received grants and personal fees from Abbott, Boston Scientific, and Terumo outside the submitted work; K.R. received grants from Norwegian Health Association during the conduct of the study. None of the other authors have conflict of interest to disclose as described by Clinical Transplantation.

AUTHOR CONTRIBUTIONS

M.R., O.G.S., L.G., B.B., N.R.H., K.N., and K.L. conceived and designed the analysis. M.R., O.G.S., K.R., and K.L. collected the data. J.D. contributed data or analysis tools. M.R., N.R.H., O.N., and K.L. performed the analysis. M.R., O.G.S., and K.L. wrote the paper. L.G., B.B., N.R.H., O.N., J.D., and K.R, reviewed and edited the paper. K.L. was responsible for funding acquisition.

DATA AVAILABILITY STATEMENT

The data are not publicly available due to strict national guidelines for privacy policy and data sharing.

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How to cite this article: Rafique M, Solberg OG, Gullestad L, et al. A randomized clinical study using optical coherence tomography to evaluate the short-term effects of high-intensity interval training on cardiac allograft vasculopathy: a HITTS substudy. *Clin Transplant*. 2022;36:e14488. https://doi.org/10.1111/ctr.14488