

Effects of high-intensity interval training on cardiac remodelling, function and coronary microcirculation in de novo heart transplant patients: a substudy of the HITTS randomised controlled trial

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ABSTRACT

Objectives High-intensity interval training (HIT) improves peak oxygen consumption (VO₂peak) in de novo heart transplant (HTx) recipients. It remains unclear whether this improvement early after HTx is solely dependent on peripheral adaptations, or due to a linked chain of central and peripheral adaptations. The objective of this study was to determine whether HIT results in structural and functional adaptations in the cardiovascular system.

Methods Eighty-one de novo HTx recipients were randomly assigned to participate in either 9 months of supervised HIT or standard care exercise-based rehabilitation. Cardiac function was assessed by echocardiogram and the coronary microcirculation with the index of microcirculatory resistance (IMR) at baseline and 12 months after HTx.

Results Cardiac function as assessed by global longitudinal strain was significantly better in the HIT group than in the standard care group (16.3±1.2% vs 15.6±2.2%, respectively, treatment effect = -1.1% (95% CI -2.0% to -0.2%), p=0.02), as was the end-diastolic volume (128.5±20.8 mL vs 123.4±15.5 mL, respectively, treatment effect=-4.9 mL (95% CI 0.5 to 9.2 mL), p=0.03). There was a non-significant tendency for IMR to indicate improved microcirculatory function (13.8±8.0 vs 16.8±12.0, respectively, treatment effect = -4.3 (95% CI -9.1 to 0.6), p=0.08).

Conclusion When initiated early after HTx, HIT leads to both structural and functional cardiovascular adaptations.

Trial registration number NCT01796379.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ High-intensity interval training compared with standard of care exercise-based rehabilitation early after heart transplantation improves peak oxygen consumption.
- ⇒ High-intensity interval training attenuates epicardial cardiac allograft vasculopathy progression in heart transplant recipients.

WHAT THIS STUDY ADDS

- ⇒ First reported evidence of cardiovascular adaptations in de novo heart transplant recipients related to exercise rehabilitation.
- ⇒ High-intensity interval training compared with standard of care exercise-based rehabilitation early after heart transplantation leads to cardiovascular adaptations and improved cardiac function.
- ⇒ High-intensity interval training may result in improved coronary microcirculatory function.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ Exercise with higher intensity than recommended by the European Society of Cardiology may be considered safe in clinically stable de novo heart transplant recipients.
- ⇒ The exercise-based rehabilitation programme in de novo heart transplant recipients should be tailored individually for each patient.
- ⇒ The relationship between exercise intensity and cardiovascular adaptations needs further investigation.



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INTRODUCTION

Previous studies have shown that peak oxygen consumption (VO₂peak) is reduced in heart transplant (HTx) recipients. More than half of HTx recipients function in New York Heart Association class II, III or IV at 1 year after HTx.¹ High-intensity interval training (HIT) in non-HTx populations has been demonstrated to be more effective than moderate-intensity continuous training

(MICT) in improving VO₂peak, preventing the onset and development of coronary artery disease and improving outcomes for patients with established cardiovascular disease.²⁻⁵ These beneficial effects of HIT are of particular interest in HTx recipients, many of whom develop hypertension, diabetes, cardiac allograft vasculopathy (CAV), left ventricular (LV) dysfunction and reduced exercise capacity.⁶⁻⁸

While exercise in HTx recipients has been recommended with caution for several decades, the High-Intensity Interval Training in De Novo Heart Transplant Recipients in Scandinavia (HITTS) trial demonstrated that early initiation of HIT in de novo HTx recipients is both safe and superior to standard care exercise-based rehabilitation in improving VO₂peak.⁹ Based on measurements of increased muscle strength, the authors concluded that the improvement in VO₂peak was mainly due to peripheral factors. However, the exercise-induced improvement in VO₂peak is usually related to structural and functional adaptations occurring within a linked chain of central and peripheral systems, including pulmonary ventilation, cardiovascular function and the ability of muscle cells to utilise oxygen.¹⁰ Although the precise mechanisms have proved elusive, exercise-induced adaptations are believed to include favourable ventricular remodelling, angiogenesis and increased blood flow capacity, all of which may lead to increased cardiac output.^{11 12} In addition, there is increasing evidence that epicardial and microvascular allograft vasculopathy can develop and progress independently and serve as independent predictors of adverse outcomes.^{13 14} HIT has been shown to attenuate epicardial CAV progression in HTx recipients, but the effect of HIT on coronary microcirculation has not been reported.^{15 16}

The global longitudinal strain (GLS) has increasingly been used to quantify LV function in clinical practice and graft monitoring due to its accuracy in detecting subclinical LV changes compared with LV ejection fraction (LVEF) and Doppler parameters.^{17 18} Coronary physiology investigations related to coronary angiography include calculations of the index of microcirculatory resistance (IMR), which is a specific and reproducible measure of microvascular function.^{19 20} Since VO₂ peak increased in the main HITTS trial, this HITTS substudy aimed to determine the HIT outcomes in structural and functional cardiovascular adaptations.

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. The study was conducted according to the Declaration of Helsinki, with written informed consent obtained from all participants.

Study population

This was a substudy of the multicentre HITTS trial in which stable de novo HTx recipients of either sex aged ≥18 years were eligible for inclusion between February 2013 and February 2017. Bicaval anastomosis was used as the surgical technique for all of the HTx patients. The design and results of the HITTS trial have been reported in detail previously.^{9 21} Within 13 weeks after HTx, 81 recipients were randomly assigned to receive 9 months of either supervised HIT or MICT. MICT is equivalent to standard care exercise-based cardiac rehabilitation as

recommended by the European Society of Cardiology.²² Similar lifestyle advice was given to recipients in the HIT and standard care groups. HIT consisted of four 4min intervals at 85%–95% of the peak effort separated by 3min of active recovery at 60%–70% of the peak effort. Standard care consisted of 25min of continuous training at 60%–80% of the peak effort. Supplementary strength training was applied equally in the two groups. Each patient completed approximately 60 exercise sessions during the intervention period.

Outcomes

The primary outcome measures were the changes in LV GLS, LV dimensions (interventricular septal thickness at end-diastole; IVSd, left ventricular posterior wall at end-diastole; LVPWd, left ventricular internal diameter at end-diastole; LVIDd) and end-diastole volume (EDV) assessed by echocardiography. The secondary outcome was the changes in the IMR and coronary flow reserve (CFR).

2D—transthoracic echocardiography

Transthoracic echocardiography was performed using a commercially available ultrasound system (GE Vivid E9 and GE Vivid E95, General Electric, Chicago, Illinois) with a 1.3–4.2MHz phased array transducer. All postprocessing analyses were performed offline by the same researcher while blinded to the interventional status using EchoPAC plug-in V.2.04 to third-party PACS, General Electric, Chicago, Illinois. LV dimensions were quantified in the parasternal view by placing callipers perpendicular to the ventricular long axis. LV mass was calculated as LV mass=0.8 (1.04(LVD+IVS+PW))³—LVD³+0.6g. Peak E-wave and peak A-wave velocities were obtained with pulsed wave (PW) Doppler between mitral leaflet tips in a four-chamber view. The mitral valve (MV) E/A ratio was calculated by dividing the E-wave velocity by the A-wave velocity. The MV deceleration time was obtained from PW Doppler between mitral leaflet tips. Stroke volume (SV) was estimated by multiplying the velocity–time integral at the LV outflow tract by the LV outflow tract area. The LV volumes were acquired tracing the LV endocardial border in apical four-chamber and two-chamber views. The change in LV volumes between end-systole and end-diastole allowed estimation of LVEF. Strains were obtained by tracing 2D speckle in images from three apical views. GLS was calculated as the mean strain of 18 segments.

Coronary physiology

Cardiac catheterisation was performed following the standard procedure at our laboratory at Oslo University Hospital, Oslo, Norway, with radial access being preferred. A pressure-temperature sensor guidewire (Certus Pressure Wire or Pressure Wire X, Abbot, Lake County, Illinois) was used for physiology measurements. A pressure measurement made using the wire was first equalised with the guiding catheter and then positioned

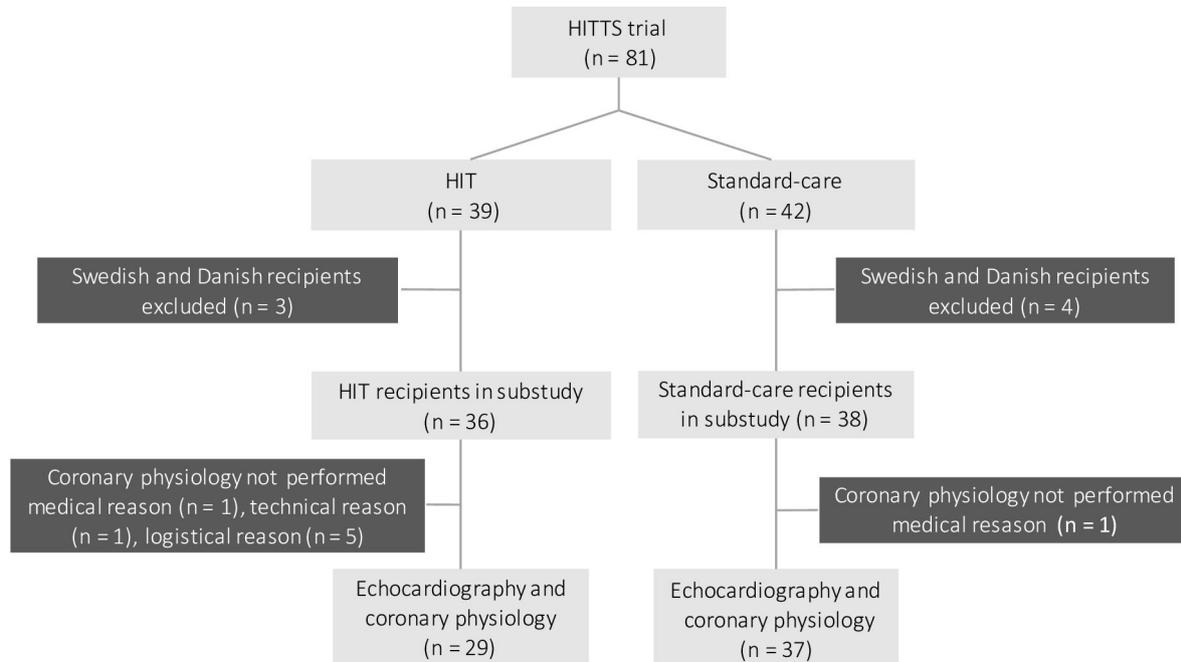


Figure 1 HIT, high-intensity interval training; HITTS, High-Intensity Interval Training in De Novo Heart Transplant Recipients in Scandinavia.

in the distal third of the left anterior descending artery. Intracoronary glyceryl trinitrate (200 µg) was administered at the beginning of the procedure and repeated if necessary. Maximum hyperemia was induced by infusing 140 µg/kg/min adenosine through a large antecubital vein. Saline (3–4 mL) at ambient temperature was injected three times or until stable measurements were acquired in the resting state and also during maximum hyperemia. The transit time of saline from the thermistor in the guidewire shaft to the distal thermistor was recorded in the resting state (T_{mnr}) and during maximum hyperemia (T_{mnh}), as were the aortic pressure (P_a) and distal coronary pressure (P_d). The coronary physiology indices were calculated as follows:

$FFR = P_d / P_a$ at maximum hyperemia (averaged over three heart beats for which its value was the lowest).

$$IMR = P_d \times T_{mnh}$$

$$CFR = T_{mnr} / T_{mnh}$$

The continuous equalisation of pressures was confirmed at the end of the procedure by repositioning the pressure wire in the ostium of the vessel. The coronary physiology measurements were made in approximately the same position in the vessel during the second heart catheterisation procedure.

Biochemical and blood pressure assessment

The blood samples were collected prior to the testing regardless of group adherence. Blood samples collected at baseline and 12 months were analysed for the complete blood cell count and by performing serum biochemical tests, including high-sensitivity C reactive protein (CRP), creatine kinase, troponin T, N-terminal pro B-type natriuretic peptide, haemoglobin, cholesterol, triglycerides and electrolytes. Serum concentrations were measured

using standard laboratory techniques. A 24-hour blood pressure measurement was carried out during the hospital stay. The equipment was removed in connection with the testing and right catheterisation.

Rejection score

The presence of cellular rejection was based on the revised version of the 1990 working formulation for the standardisation 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.²³ The rejection score was calculated as (number of grade-1-R rejections)×1 + (number of grade-2-R rejections)×2 + (number of grade-3-R rejections)×3.

Statistical analyses

All data were analysed using standard statistical software (Stata/SE V.16, Stata Corporation, College Station, Texas). Histograms and Q-Q plots were used to check whether continuous variables conformed to a normal distribution; those that did are reported as mean±SD or median with IQR values. Baseline variables were compared using the t-test or Mann-Whitney U test as appropriate. Categorical data are presented as absolute values with percentages. Baseline variables were compared using the χ^2 test or Fisher's exact test as appropriate. Mixed-effects multilevel regression was used to detect treatment effects in repeated measurements. All reported p values were two-sided, and the threshold for statistical significance was set at $p < 0.05$.

RESULTS

Patient population

In the multicentre HITTS trial, coronary physiology measurements were planned only in HTx recipients from Oslo University Hospital, Rikshospitalet, Oslo, Norway, and they were eligible for enrolment in the current substudy. Patients who were included for the main HITTS trial at Sahlgrenska University Hospital, Gothenburg, Sweden and at Rikshospitalet, Copenhagen, Denmark were excluded from the current substudy. This criterion resulted in the inclusion of 74 recipients. [Figure 1](#) displays a flowchart of the participants. There were more recipients with coronary physiology measurements in the standard care group (n=37) than in the HIT group (n=29). Examinations were missed at random in each group, and, hence, this did not result in selection bias. The adherence to training was 94% in the HIT group and 97% in the Standard care group. The mean exercise session bout in the HIT group increased from 2.3±0.7 min

in the first period to 3.6±0.7 min in the last period. The mean length of the exercise session in the Standard care group was 56±13 min throughout the intervention period. Transthoracic echocardiogram images obtained at baseline and 12 months were available for all of the included HTx recipients. None of the recipients were lost to follow-up. There were no severe complications related to any of the procedures in the study, and all of the included patients were alive after 12 months of follow-up.

Baseline characteristics

None of the clinical characteristics and medication differed significantly between the groups at baseline ([table 1](#)). Five (8%) of the recipients had undergone previous HTx. The leading cause of HTx was dilated cardiomyopathy (42%). The recipients were aged 52 (40–58) years and 47 (71%) of them were men, while the donors were aged 33 (23–48) years and 45 (68%) of them were men. The cold ischaemic time was 211

Table 1 Patient characteristics and medications at baseline

	HIT (n=29)	Standard care (n=37)	P
Characteristic			
Age of donor, years	29 (22 to 46)	34 (29 to 48)	0.25
Sex of donor, male	19 (66)	26 (70)	0.68
Cold ischaemic time, min	205 (92 to 235)	214 (95 to 245)	0.56
Age of recipient, years	52 (42 to 58)	52 (40 to 57)	0.90
Sex of recipient, male	20 (69)	27 (73)	0.72
LVAD	4 (14)	6 (16)	0.79
Reason for transplantation			0.22
DCM	14 (48)	14 (38)	
ICM	9 (31)	8 (22)	
Other	6 (21)	15 (41)	
Immunosuppressant			
Cyclosporine	20 (69)	28 (76)	0.54
Tacrolimus	9 (31)	9 (24)	0.54
Everolimus	10 (34)	11 (30)	0.68
Mycophenolate	26 (90)	33 (89)	1.00
Prednisolone	29 (100)	37 (100)	1.00
Medication at baseline			
Antiplatelet agents	4 (14)	4 (11)	0.72
Anticoagulation	4 (14)	2 (5)	0.39
Beta-blockers	8 (28)	11 (30)	0.85
ACE inhibitors	0 (0)	1 (3)	1.00
Angiotensin-receptor blockers	2 (7)	1 (3)	0.58
Statins	28 (97)	37 (100)	0.44
Diuretics	25 (86)	31 (84)	1.00

Data are n (%), median (IQR), or mean±SD values. p values are for between-groups comparisons at baseline.

ACE, angiotensin-converting enzyme; DCM, dilated cardiomyopathy; HIT, high-intensity interval training; ICM, ischaemic cardiomyopathy; LVAD, left ventricular assist device.

(94–240) min. Standard immunosuppressive medication was given according to local protocols. Forty-eight (73%) of the patients were treated with cyclosporine, 18 (27%) were treated with tacrolimus and 21 (32%) were treated with everolimus. All except one of the recipients were using statins. The body mass index (BMI) at the time of inclusion was 25±4 kg/m².

Transthoracic echocardiography

Analysis of GLS reproducibility showed good to excellent intraobserver and interobserver agreement levels. The intraclass correlation coefficient (ICC) for intrarater reliability was 0.99 (95% CI 0.95 to 0.99) and ICC for inter-rater reliability was 0.88 (95% CI 0.60 to 0.97). The failure rate for analysing GLS was 22%. The average framerate of images that was analysed for GLS was 59.8 frames/s. Manual contour adjustment was performed and optimised for all patients.

The treatment effect on LV morphology is presented in [table 2](#). The GLS and LV end-diastolic volume (LVEDV)

were significantly higher in the HIT group than in the standard care group. The treatment effect on GLS was -1.1% (95% CI -2.0% to -0.2%, p<0.05), and that on LVEDV was 4.9 mL (95% CI 0.5 to 9.2 mL, p<0.05). There were significant changes in LV end-diastolic dimensions in the standard care group, including in the IVSd, LVPWd, LVIDd, and LVPWd in the HIT group.

The LV end-diastolic dimensions decreased significantly in the overall study population: IVSd from 10.4±1.6 mm to 10.2±1.4 mm (change=0.3 mm, (95% CI 0.1 mm to 0.4 mm, p<0.05), LVPWd from 9.1±1.1 mm to 8.9±1.1 mm (change=0.3 mm), (95% CI 0.1 mm to 0.4 mm, p<0.05) and LVIDd from 48.5±4.4 mm to 47.9±4.7 mm (change=0.6 mm) (95% CI 0.3 mm to 1.0 mm, p<0.05). The heart rate (HR), SV, cardiac mass, cardiac index and diastolic function parameters did not change significantly. There was no significant correlation between VO₂peak and GLS at 12 months ($r=-0.13$, p=0.42).

Table 2 Transthoracic echocardiography

	HIT		Standard care		Treatment effect	P
	n=29		n=37			
	Baseline	12 months	Baseline	12 months	Change (95% CI)	
Dimensions						
IVSd (mm)	10.2±1.5	9.9±1.3	10.6±1.6	10.3±1.5*	0.03 (-0.28 to 0.33)	0.86
LVPWd (mm)	9.1±1.3	8.9±1.2*	9.2±1.0	8.9±1.0*	0.03 (-0.26 to 0.32)	0.83
LVIDd (mm)	48.4±4.8	48.3±5.0	48.6±4.1	47.6±4.4*	0.6 (-0.1 to 1.3)	0.09
IVSs (mm)	13.8±1.3	13.7±1.2	14.1±1.3	14.3±2.3	-0.3 (-0.9 to 0.4)	0.43
LVPWs (mm)	14.7±1.4	14.6±1.2	14.8±1.2	14.7±1.1	0.1 (-0.1 to 0.4)	0.32
LVIDs (mm)	31.9±2.7	32.1±3.2	31.5±3.4	31.1±3.4	0.5 (-0.1 to 1.2)	0.12
LVM ACE (gr)	157.3±28.9	158.5±30.5	157.6±25.4	153.7±26.7	4.6 (-1.6 to 10.8)	0.14
LVMi ACE (gr)	81.8±12.9	80.7±13.5	82.0±10.6	79.3±12.1	1.8 (-2.0 to 5.6)	0.35
Diastolic function						
EA-ratio	1.88±0.37	1.86±0.39	1.92±0.63	1.86±0.38	0.02 (-0.22 to 0.26)	0.88
IVRT (ms)	85±14	83±12	87±13	89±15	-3.0 (-9.6 to 3.5)	0.37
EdecT (ms)	162±28	158±27	165±27	160±29	3.1 (-14.1 to 18.4)	0.79
Systolic function						
HR (beats/min)	88±11	89±12	82±11	87±11	-3.5 (-8.7 to 1.7)	0.19
SV (mL)	66.5±13.8	66.4±14.8	72.5±14.3	69.6±14.4	2.6 (-1.3 to 8.9)	0.15
CO, L/min	5.8±1.2	5.8±1.1	5.9±1.1	5.9±1.0	0.09 (-0.27 to 0.46)	0.62
CI, L/min/m ²	3.1±0.5	3.0±0.6	3.1±0.5	3.0±0.5	-0.003 (-0.208 to 0.201)	0.97
EF Biplan (%)	54±3	54±3	55±3	54±2*	1.1 (-0.2 to 2.3)	0.09
GLS (%)	15.8±1.7	16.3±1.2	16.1±2.2	15.6±2.2	-1.1 (-2.0 to -0.2)	0.02
EDV (mL)	128.2±19.0	128.5±20.8	128.0±16.3	123.4±15.5*	4.9 (0.5 to 9.2)	0.03
ESV (mL)	60.0±10.0	59.3±10.9	57.6±7.8	56.7±7.5	-0.2 (-2.8 to 2.5)	0.91

Data are mean±SD values or mean (95% CI). p values are from mixed-effects multilevel regression and are for between-groups comparisons. *P<0.05 within group.

CI, cardiac index; CO, cardiac output; EdecT, e deceleration time; EDV, end diastolic volume; EF, ejection fraction; ESV, end systolic volume; GLS, global longitudinal strain; HIT, high-intensity interval training; IVRT, isovolumic relaxation time; IVSd, interventricular septal end diastole; IVSs, interventricular septal end systole; LVIDd, left ventricular internal diameter end diastole; LVIDs, left ventricular internal diameter end systole; LVM, left ventricular mass; LVMi, left ventricular mass index; LVPWd, left ventricular posterior wall end diastole; LVPWs, left ventricular posterior wall end systole; SV, stroke volume.

Table 3 Coronary physiology measurements

	HIT		Standard care		Treatment effect Change (95% CI)	P
	n=29		n=37			
	Baseline	12 months	Baseline	12 months		
Clinical features						
IMR	14.8±9.5	13.8±8.0	13.8±5.8	16.8±12.0	-4.3 (-9.1 to 0.6)	0.08
FFR	0.92±0.04	0.93±0.05	0.92±0.05	0.93±0.05	0.007(-0.02 to 0.04)	0.61
CFR	4.0±2.5	4.8±2.9	4.2±2.1	4.1±1.9	0.8 (-0.8 to 2.3)	0.32

Data are mean±SD values or mean (95% CI). P values are from mixed-effects multilevel regression and are for between-groups comparisons.
CFR, coronary flow reserve; FFR, fractional flow reserve; HIT, high-intensity interval training; IMR, index of microvascular resistance.

Quantitative coronary physiology assessment

The results of the coronary physiology assessment are presented in [table 3](#). IMR improved in the HIT group and worsened in the standard care group. The difference in the IMR change between the two treatment arms was -4.3 mm Hg·s (95% CI -9.1 to 0.6 mm Hg·sec, $p=0.08$). CFR increased in the HIT group but remained virtually unchanged in the standard care group (change=0.8, 95% CI -0.8 to 2.3, $p=0.32$). The difference in fractional flow reserve between the groups was negligible. There was no significant correlation between VO_{2peak} and IMR after 12 months ($r=0.24$, $p=0.08$), or between IMR and GLS ($r=0.26$, $p=0.12$). However, in a linear regression model, IMR was significantly related to LVEF ($r=-0.37$, $p<0.05$).

Exploratory variables

The exploratory variables are compared between groups in [table 4](#). BMI, 24-hour blood pressure measurements, and CRPs were significantly higher in the HIT group than in the standard care group.

DISCUSSION

This substudy of the randomised controlled HITTS trial has demonstrated that initiating HIT early after HTx results in improved LV function as assessed by GLS and a change in IMR that indicates improved microcirculatory function.

HIT was more effective than standard care in improving VO_{2peak} in the main HITTS trial.⁹ There was no difference between the exercise groups in the measured echocardiography and right catheterisation variables. As a result of improved muscle strength, the authors concluded that peripheral factors played a central role in improving VO_{2peak} . Using the oxygen pulse as a surrogate marker for SV, the authors suggested that central factors were also involved in improving VO_{2peak} . However, the results of the HITTS trial were based on non-dedicated routine echocardiography, and GLS was not analysed despite this parameter being independently correlated with VO_{2peak} and superior to LVEF for identifying patients with reduced aerobic capacity.²⁴ GLS is

less operator dependent, more reproducible and more sensitive than LVEF for evaluating LV function.^{25 26}

The temporal changes in LV morphology early after HTx are characterised by increases in LV wall thickness and mass due to inflammatory cell infiltration and graft oedema, which decrease successively during the first year. Although there is no description in the literature of cardiovascular adaptation arising from HIT in de novo HTx recipients, previous studies in athletes have suggested two different types of cardiac remodelling: (1) eccentric remodelling that results from volume load in endurance training with thickening of the LV wall and LV dilatation and (2) concentric remodelling resulting from pressure load in resistance training with increased myocardial mass and wall thickness without LV dilatation.^{27 28} Given that the wall thickness, including IVSd and LVPWd in the standard care group, reduced as expected, whereas IVSd remained unchanged in the HIT group, our findings in the latter group indicate the presence of cardiac remodelling without a single specific mechanism. However, given the significant intergroup difference in LVEDV, our findings suggest that HIT in de novo HTx recipients is closer to eccentric remodelling than concentric remodelling.

The increases in maximum HR in the HITTS trial were similar in the HIT and standard care groups.⁹ Thus, an increased cardiac output induced by HIT would be explained by an increased SV due to a larger ventricular volume or improved contractile function. A study evaluating the LV volume in endurance athletes using contrast echocardiography found that a large increase in SV in endurance athletes could be explained by an almost linear increase in LVEDV.²⁹ Although the difference in SV between groups did not reach statistical significance, the GLS and LVEDV were both significantly higher in the HIT group than in the standard care group. Increased BP is associated with reduced GLS.³⁰ Both the systolic and diastolic BP increased significantly in the HIT group, while it remained unchanged in the standard care group. In addition, the BP was significantly higher in the HIT group than in the standard care group at follow-up.

Table 4 Exploratory variables

	HIT		Standard care		Treatment effect Change (95% CI)	P
	n=29		n=37			
	Baseline	12 months	Baseline	12 months		
Clinical features						
Weight, kg	75±13	81±16*	78±15	81±17*	2.9 (0.02 to 5.86)	0.05
Body mass index, kg/m ²	24.4±3.3	26.4±4.0*	25.3±3.9	26.3±4.3*	1.0 (0.1 to 2.0)	0.04
Systolic BP, mm Hg	131±10	139±11*	133±13	135±15	6.7 (0.5 to 12.9)	0.03
Diastolic BP, mm Hg	79±5	86±6*	81±8	83±11	5.1 (1.0 to 9.1)	0.01
Biochemistry						
CRP, mg/L	2.7 (1.0 to 4.2)	2.0 (0.6 to 5.5)	2.3 (0.9 to 6.7)	2.0 (0.6 to 3.8)	8.2 (0.6 to 15.8)	0.03
HbA1c, %	5.5 (5.1 to 6.4)	5.8 (5.2 to 6.8)	5.4 (5.0 to 6.0)	5.5 (5.2 to 5.8)	0.3 (−0.1 to 0.6)	0.12
Total cholesterol, mmol/L	5.0 (4.6 to 5.8)	5.1 (4.5 to 5.5)	4.8 (4.3 to 5.7)	4.5 (3.7 to 6.1)	−0.1 (−0.8 to 0.6)	0.78
LDL cholesterol, mmol/L	2.8 (2.3 to 3.5)	2.9 (2.4 to 3.2)	2.7 (2.1 to 3.1)	2.4 (2.0 to 3.3)	−0.2 (−0.6 to 0.3)	0.43
HS-troponin T, ng/L	27 (19 to 66)	11 (7 to 20)*	33 (20 to 56)	13 (8 to 27)*	−1.0 (−17.4 to 15.5)	0.91
NT-proBNP, pmol/L	100 (64 to 217)	42 (14 to 61)*	108 (74 to 173)	28 (19 to 58)*	−43 (−102 to 15)	0.15
Creatinine, µmol/L	117±35	99±21*	119±29	104±28*	−2.7 (−14.5 to 9.1)	0.65
Rejection score						0.38
0	19 (66)	18 (62)	22 (59)	17 (46)		
1	6 (21)	5 (17)	7 (19)	9 (24)		
2	1 (3)	2 (7)	4 (11)	6 (16)		
3	2 (7)	2 (7)	1 (3)	0		
4	0	1 (3)	1 (3)	1 (3)		
5	0	0	2 (5)	2 (5)		
6	1 (3)	0	0	2 (5)		
7	0	0	0	0		
8	0	1 (3)	0	0		
Peak oxygens consumption, L/min	1.5±0.4	2.0±0.6*	1.6±0.4	2.0±0.6*	0.2 (−0.01 to 0.33)	0.06
Right heart catheterisation						
RAP, mm Hg	5±3	4±3	5±3	4±3*	0.7 (−1.2 to 2.6)	0.46
PCWP, mm Hg	13±6	10±5*	11±5	10±5	−1.5 (−4.0 to 1.1)	0.27
CO, L/min	7.0±1.7	7.0±1.9	6.6±1.7	6.9±1.5	−0.2 (−1.0 to 0.6)	0.59
CI, L/min/m ²	3.9±1.1	3.7±0.8	3.4±0.8	4.1±3.5	−1.0 (−2.3 to 0.5)	0.20

Data are n (%), median (IQR), or mean±SD values. P values are from mixed-effects multilevel regression and are for between-groups comparisons.

*P<0.05 within group.

CAV, cardiac allograft vasculopathy; CRP, C reactive protein; HbA1c, glycated haemoglobin; HIT, high-intensity interval training; HS, high sensitivity; LDL, low-density lipoprotein; NT-proBNP, N-terminal pro-brain natriuretic peptide.

These results suggest that HIT in de novo HTx recipients leads to remodelling of the left ventricle and (most likely) increased cardiac output as one of the mechanisms for the increased VO₂peak observed in the HITTS trial.

Microvascular dysfunction is associated with the development of heart failure with a reduced LVEF in patients with diabetes, HT and hypertrophic cardiomyopathy.³¹ Vasodilatory capacity decreases and microvascular resistance increases as the heart ages, but the effects of exercise training on microvascular function in humans

have not been studied extensively, especially for HTx recipients.^{32–37} In a rat model, exercise training was shown to reduce the age-related decline in microvascular function.³⁸ In the current study, microvascular function as assessed with IMR and CFR improved in the HIT group but not in the standard care group during the first year after HTx. Although the difference between groups did not reach statistical significance, this tendency suggests that HIT improves coronary microcirculation compared with standard care.

In HTx recipients, the mean capillary density is only about half of that in non-HTx controls, which may significantly impact total microcirculatory resistance.³⁹ Microvascular CAV is a concentric medial disease that affects more than 40% of HTx recipients, and it may also substantially impact microcirculatory resistance.³⁹ However, exercise leads to adaptations in the myocardium that increases the maximum cardiac output and the maximum total body oxygen consumption.⁴⁰ According to Duncker and Bache, exercise training is associated with adaptations in the coronary microvasculature, including increased arteriolar densities and diameters, and functional adaptations such as changes in neuro-humoral control mechanism or in local vascular control mechanism, which all may contribute to increased oxygen supply to the myocardium.⁴¹ Our results indicate that HIT is an effective intervention to stimulate some or all of these mechanisms.⁴²

Leung *et al* showed that LV contractile reserves as measured with low-dose dobutamine, echocardiography can be used to estimate IMR non-invasively, and that an impaired contractile reserve indicates microvascular dysfunction.⁴³ In contrast, Kobayashi *et al* found that IMR does not correlate with GLS at 1 year after HTx, and that IMR and GLS may be used as independent predictors of late death or repeated HTx.⁴⁴ In accordance with this, we also found that there was no correlation between IMR and GLS, and it seems like that the beneficial effects of HIT on LV function and the coronary microcirculation are mediated via different and independent mechanisms.

Our study had several limitations. The required sample size was primarily calculated for VO₂peak in the main HITTS trial.²¹ This resulted in a small sample that restricted the statistical power of our results and may have resulted in type II errors, in particular, for the primary outcome of coronary physiology measurements. Also, the study protocol was prespecified and designed to only determine the effects of HIT on cardiac function and the coronary microcirculation. A better understanding of the mechanism underlying the improved IMR could have been obtained by reinvestigating myocardial biopsies. An improvement in VO₂peak is usually expected after HTx, and it is unclear whether all of the observed improvements in our trial were caused by the exercise intervention rather than representing the natural course after HTx, since there was no control group.

CONCLUSION

This study found that early initiation of HIT in de novo HTx recipients results in beneficial adaptations of the cardiovascular system characterised by higher GLS, higher LVEDV and probably also improved microvascular function.

Contributors MR, OGS, LG, BB, KN, KM and KL conceived the study and designed the analysis method. MR, OGS, KR and KL collected the data. MR, OGS and KL performed the analyses. MR, OGS and KL drafted the paper. LG, BB, KR and KM reviewed and edited the paper. KL was responsible for funding acquisition. MR and KL are responsible for the overall content.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by South-East Regional Committee for Medical and Health Research Ethics in Norway (ref number: 2012/2305). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. The data are not publicly available due to strict national guidelines on privacy policies and data sharing.

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