



**High-intensity interval training in *de novo* heart
transplant recipients with long-term follow-up**

Thesis for the degree of Philosophiae Doctor (PhD)

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2021



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*Series of dissertations submitted to the
Faculty of Medicine, University of Oslo*

ISBN 978-82-8377-890-8

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Acknowledgements

The most important contributors to this project are all the heart transplant recipients. Thank you for your willingness to be included into this project just a few months after you received your new heart. I am impressed with all the hard work you have done throughout these three years.

This project has been a multidisciplinary project with dedicated personnel from different disciplines at Oslo University Hospital, Rikshospitalet, Sahlgrenska University Hospital, Gothenburg, Rigshospitalet, Copenhagen, and physical therapists outside the hospitals, and I thank you all for the good cooperation.

I would also like to thank the Norwegian Health Association for my PhD grant.

I have been surrounded many people who not only helped me to gain scientific knowledge of high quality, but also contributed to my personal growth as a researcher in a broader perspective.

First, I give my gratitude to my supervisors Kari Nytrøen, Lars Gullestad and Arne K. Andreassen. Kari, my main supervisor, gave me the opportunity to continue in her footsteps in the field of exercise after heart transplantation. Her expertise in this field is unique and I feel extremely lucky that I have had her as my mentor since 2008 when I was a master's student. Kari has a personality of empathy and courage, and I know who to ask when I need advice to make difficult decisions. I am forever thankful of the way she has guided me through these years as a PhD student. Lars included me into his research group when I was a research assistant. I am so thankful that he gave me the opportunity to continue as a PhD student in his group. Lars is a generous person, and his work capacity is enormous, he is a true role model. His engagement and the way he inspire me to achieve higher goals have always motivated me to try new things. Arne has a great ability to clarify research topics and to say things to the

point. He has helped me to draw the “big lines” in the research project when I have struggled with details, which I really appreciate. Kaspar Broch has also acted as a supervisor for me with his prompt feedback on manuscripts and abstracts. I always learn something new in discussions with him. In addition, he often stops by our office asking, “how are you doing?” Marianne Yardley, my main fellow at the HITTS 1-year follow-up study. She was a pleasure to work with, and I still miss the exercise tests we did together at the lab and the discussions we had at the office.

The transplant nurses, Anne R. Authen, Ingelin Grov, Gry Tjønnås and Marit R. Kunszt, with their years of expertise taking care of heart transplant recipients, have been essential to the HITTS project. We could not manage to do this study without you. Research nurse Elisabeth Bjørkelund’s systematic and practical skills of how to run research projects and especially taking care of the biobank in the HITTS study is outstanding. Thanks to co-author and consultant cardiologist, Einar Gude, for always being supportive and for being available for clinical questions at any time. Co-author Kjell Ingar Pettersen, who introduced me to the field of health-related quality of life research has been an important contributor to my interest and understanding of this topic. Dag Olav Dahle, performed all the tests of endothelial function in the HITTS 1-year follow-up study, thank you for your effort and kind cooperation. Thanks to the Scandinavian collaborators and the co-authors Julia P. Wigh and Kristian Karason at Sahlgrenska University Hospital, Gothenburg and Christian H. Dall and Finn Gustafsson, Rigshospitalet, Copenhagen. I appreciate the collaboration with you.

My dear friends and PhD fellows in the office, Amjad Hussain, Andreas Auensen, Anette B. Kvaslerud, Kristine V. B. Englund, Anne K. Anstensrud and Cristiane Mayerhofer, thank you all for making the years spent in the office a very pleasant place to be. Amjad, especially thanks to you for joining me on my runs around Sognsvann. Øyvind S. Andersen, my college and friend, I am so grateful of our friendship throughout these years as a PhD student sharing

literature, music, and interests outside research. A special thanks to the social worker at the heart transplant team, Kari Raftevoll Grodås, for all the good conversations and for always showing interest in my research. To my physical therapy colleagues, I am grateful for your support. Thanks to my leaders Torhild Birkeland and Steinar Krey Voll at the Department of Clinical Service for given me the opportunity to do my PhD education in combination with my clinical work as a physical therapist.

Research has been a big part of my life during these years as a PhD student and in some periods, I have been more at the office than at home. Thanks to my dear neighbors and “Nabolaget” for care, support, and laughter in my everyday life. To my close friend, Ida Gulowsen, thank you.

Finally, a big thanks to my dear family. My father, for always showing interest in what I have been doing, from the little everyday moments to bigger happenings. The daily phones and messages wishing me good luck, they have meant a lot throughout these years. To my mother, I know she would have been so proud of me and I wish I could have shared all my experiences with her today, I miss her. My big sisters, Gry Pernille and Benedicte, as they always being there for me when needed. My nieces, Martine, Pernille, Alva and my nephews, Mathias, Even, Oscar, they are sunshine in my life.

Illustrations

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List of abbreviations

6 MWT, 6-minute walking test

AMR, antibody mediated rejection

Ang-2, angiopoietin-2

ASD, atrial septal defect

AT, anaerobic threshold

a-vO₂ diff, arteriovenous oxygen difference

BDI, Becks Depression Inventory

BIA, bioelectrical impedance analysis

CABG, coronary artery bypass grafting

CAS, Control Attitude Scale

CAV, cardiac allograft vasculopathy

CMV, cytomegalovirus

CPET, cardiopulmonary exercise test

EQ-5D, Euroqol-5D

FMD, flow mediated dilatation

HADS, Hospital Anxiety and Depression Scale

HIT, high-intensity interval training

HITTS, High-intensity Interval Training in De Novo Heart Transplant Recipients in

Scandinavia

HRR, heart rate reserve

HRQoL, health-related quality of life

HTx, heart transplantation/heart transplant

ISHLT, International Society for Heart and Lung Transplantation

KCCQ, Kansas City Cardiomyopathy Questionnaire

METs, metabolic equivalents

MICT, moderate intensity continuous training

MLHFQ, Minnesota Living with Heart Failure

MWT, minute walking test

NT-ProBNP, N-terminal pro-B-type natriuretic peptide

RCT, randomized controlled trial

RER, respiratory exchange ratio

RPE, rated perceived exertion

SD, standard deviation

SF-36v2, Short-Form-36 version 2

STAI, Stait-Track Anxiety Inventory

PAT, arterial tonometry

QoL, quality of life

TEX, Transplant Exercise

WHOQOL-BREF, brief version of the World Health Organization Questionnaire on Quality of Life

VAS, visual analogue scale

VEGF-1, vascular endothelial growth factor

VO_{2peak}, peak oxygen consumption

Norsk sammendrag

Hjertetransplanterte pasienter har et redusert oksygenopptak sammenlignet med den generelle befolkningen. Det er tidligere vist at oksygenopptak er assosiert med overlevelse hos hjertetransplanterte, det er derfor viktig å finne metoder som kan bidra til økt oksygenopptak. Trening med moderat intensitet er standardbehandling i rehabiliteringen etter hjertetransplantasjon. Høy-intensitetsintervalltrening (HIT) er en forholdsvis ny og mindre utprøvd metode i denne pasientgruppen. I de få randomiserte kontrollerte studiene som finnes har HIT vist seg å være en effektiv metode for å øke oksygenopptaket hos hjertetransplanterte > 1 år etter transplantasjonen. Hos nylig hjertetransplanterte (< 1 år etter transplantasjonen) har denne treningsmetoden derimot vært frarådet på grunn av det denerverte hjertet. Disse restriksjonene har hovedsakelig vært basert på antakelser, og det foreligger ikke vitenskapelige studier på området.

Hva som er mekanismene bak det reduserte oksygenopptaket hos hjertetransplanterte pasienter, er ikke helt klarlagt. Mye tyder på at det er perifere faktorer (muskelstyrke, endotelfunksjon, kroppssammensetning) mer enn de sentrale (hjertefunksjon) som er med å på å predikere oksygenopptaket hos hjertetransplanterte utover i forløpet (> 1 år etter transplantasjonen), mens dette i mindre grad er undersøkt hos nylig hjertetransplanterte pasienter.

Hovedmålene med denne doktorgraden var:

1. Undersøke prediktorer for oksygenopptaket hos nylig hjertetransplanterte pasienter.
2. Sammenligne effekten av HIT versus moderat trening på arbeidskapasiteten hos nylig hjertetransplanterte pasienter med 1-års oppfølging.
3. Sammenligne effekten av HIT versus moderat trening på helse relatert livskvalitet hos nylig hjertetransplanterte pasienter med 1-års oppfølging.

4. Sammenligne langtidseffekter av HIT versus moderat trening på arbeidskapasiteten hos nylig hjertetransplanterte.

Hele grunnlaget for denne avhandlingen er HITTS studien (High-intensity Interval Training in De Novo Heart Transplant Recipients in Scandinavia). Dette var en prospektiv, randomisert kontrollert multisenterstudie med deltakere fra Oslo universitetssykehus, Rikshospitalet (hovedsenter), Sahlgrenska universitetssykehus, (Gøteborg) og Rigshospitalet (København). Deltakerne ble inkludert 7–16 uker (gjennomsnitt 11 uker) etter hjertetransplantasjonen og ble randomisert 1:1 enten til HIT (85–95% av maksimal anstrengelse) eller moderat trening (< 80% av maksimal anstrengelse). Treningsintervensjonene varte i ni måneder under veiledning av lokale fysioterapeuter i deltakernes hjemkommuner. I tillegg til kondisjonstreningen, trente deltakerne i begge grupper generell styrketrening. Alle de veiledede treningsøktene ble loggført og monitorert med pulsklokke.

Alle studietester og undersøkelser ble utført på studiesenteret ved baseline, ett år og tre år etter hjertetransplantasjonen. Ved 3-års oppfølgingen deltok kun den norske populasjonen. Det primære endepunktet i studien var oksygenopptak målt på tredemølle eller sykkel. Sekundære endepunkter var muskelstyrke i bena (dynamometer), kroppssammensetning (bioelektrisk impedansanalyse), hjertefrekvensrespons (belastningstest), hjertefunksjon (ekkokardiografi), biomarkører, hemodynamiske mål (høyre hjertekateterisering, blodtrykk), endotelfunksjon (EndoPAT, flow-mediert dilatasjon), helserelatert livskvalitet (Short-Form-36 versjon 2 (SF-36v2)), symptomer på angst og depresjon (the Hospital Anxiety and Depression Scale (HADS)), sikkerhet og uønskede (alvorlige) hendelser. Ved 3-års oppfølgingen fikk deltakerne i tillegg en aktivitetsmåler (i 7 dager) og et spørreskjema om fysisk aktivitet. Mellom 1-års og 3-års oppfølging var det ingen spesifikk trening, men deltakerne ble oppfordret til å fortsette med valgfri trening og fysisk aktivitet på egenhånd.

I den første artikkelen i avhandlingen undersøkte vi prediktorer for oksygenopptak hos nylig hjertetransplanterte pasienter inkludert i HITTS studien. Åttien deltakere ble inkludert og gjennomsnittsalderen \pm standardavviket i hele populasjonen var 49 ± 13 år, 73% var menn. Populasjonen hadde et gjennomsnittlig oksygenopptak på 20.4 mL/kg/min som var 56% av forventet sammenlignet med den generelle befolkningen. Det var sterke korrelasjoner mellom oksygenopptaket (L/min) og hjerterefrekvensreserve, O₂ puls og utholdende muskelstyrke. I en multipel regresjonsanalyse forklarte O₂ puls, hjerterefrekvensreserve, utholdende muskelstyrke, kroppsmasseindeks, kjønn og alder 84 % av variasjonen i oksygenopptaket.

Artikkel to i avhandlingen viste effekten av HIT versus moderat trening fra 1-års oppfølgingen i HITTS studien. Syttiåtte av 81 deltakere (96%) fullførte studien. Det var ingen alvorlige hendelser relatert til treningsøktene i noen av gruppene.

Etter 9 måneder med trening var forskjellen i endring i oksygenopptak signifikant i favør HIT gruppen. Forskjellen i oksygenopptak på 1.8 mL/kg/min tilsvarte 0.5 metabolske ekvivalenter og var en klinisk viktig forskjell. Det var også signifikante forskjeller i endring i anaerob terskel (AT), maksimal ekspiratorisk luftstrøms hastighet og utholdende muskelstyrke i bena i favør HIT gruppen.

I den tredje artikkelen undersøkte vi mer inngående effekten av HIT versus moderat trening på helserelatert livskvalitet i en substudie av 1 års oppfølgingen i HITTS studien. Resultatene viste at begge grupper økte de fysiske domenene i helserelatert livskvalitet (SF-36 v2) signifikant i løpet av intervensjonsperioden. Deres mentale helse målt med SF-36v2 og HADS var god ved baseline og holdt seg stabil gjennom hele intervensjonsperioden. På subskalaen emosjonell rolle funksjon i SF-36 var det en gjennomsnittlig større positiv endring i skår i favør HIT gruppen, mens det var ingen forskjeller mellom gruppene på de sju andre subskalaene. Bedre selvrapporert fysisk funksjon var assosiert med høyere oksygenopptak og muskelstyrke.

Den fjerde artikkelen i avhandlingen viste resultatene fra 3-års oppfølgingen i HITTS studien. Sekstito deltakere fullførte studien tre år etter hjertetransplantasjonen, 76% var menn. Det var ingen forskjell mellom HIT versus moderat trening i endringen i oksygenopptak fra baseline til 3-års oppfølging. Oksygenopptaket mellom 1-års og 3-års oppfølging var stabilt i begge grupper med kun en numerisk nedgang i begge grupper. Endringene fra baseline til 3-års oppfølging i utholdende muskelstyrke og AT var fortsatt signifikant i favør HIT gruppen. Den helserelevante livskvaliteten var god i begge grupper tre år etter hjertetransplantasjonen. Flertallet i begge grupper var i gjennomsnitt mer enn i 30 minutter daglig fysisk aktivitet med moderat intensitet. Kun et fåtall var fysisk aktive med høy intensitet. Det var ingen forskjeller mellom gruppene i fysisk aktivitetsnivå målt med objektive mål og selvrapporing.

Hovedkonklusjonene i denne doktorgradsavhandlingen var:

1. Prediktorer for oksygenopptaket hos nylig hjertetransplanterte så ut til å være både sentrale og perifere faktorer.
2. HIT var trygt å gjennomføre utenfor sykehus under veiledning av fysioterapeuter lokalt. HIT var en mer effektiv metode enn moderat trening for å øke den fysiske kapasiteten hos nylig hjertetransplanterte pasienter. I tillegg hadde HIT en større økning i AT, ekspiratorisk maksimal ekspiratorisk luftstrøms hastighet og utholdende muskelstyrke sammenlignet med moderat trening. Analyser innad i hver gruppe, viste at moderat trening også førte til økt oksygenopptak, og bekrefter den etablerte kunnskapen om de positive effektene av det eksisterende hjerterehabiliteringstilbudet.
3. Både HIT og moderat trening økte de fysiske domeneene i helserelevante livskvalitet, mens den mentale helsen var god og stabil i begge grupper i løpet av intervensjonsperioden..
4. Funnene fra 3-års oppfølgingen viste at det ikke var noen vedvarende effekt av HIT sammenlignet med moderat trening på oksygenopptaket som vist ved 1-års oppfølgingen. På

de sekundære endepunktene muskelstyrke og AT var det fortsatt en signifikant forskjell i endring i favør HIT gruppen. Den helse relaterte livskvaliteten var god i begge grupper tre år etter hjertetransplantasjonen.

Systematisk trening tidlig etter en hjertetransplantasjon kan bidra til enkelte gode fysiske aktivitetsvaner, mens det kan synes som HIT uten veiledning var for krevende å utføre over tid. Med mål om å oppnå bedre etterlevelse av HIT på lengre sikt etter en hjertetransplantasjon, bør fremtidige studier undersøke effekten av ulike HIT protokoller (kortere varighet eller færre repetisjoner).

Preface

Exercise, as a part of the rehabilitation program after heart transplantation (HTx), has been prescribed for years and is not a new idea for this population. However, there has been a lack of randomized controlled trials of the effects of exercise after HTx, and there has been no consensus on *how*, *when* and at *what intensity* exercise should be performed. Medical treatment after HTx is based on the best available evidence-based knowledge, which should also be the case for exercise as medicine after HTx. In recent years, this topic has gained more attention.

When I started in 2013 with the first participant in the HITTS (High-intensity Interval Training in de Novo Heart Transplant Recipients in Scandinavia) trial, I was curious and excited at the same time. The HITTS study was the first of its kind to ever do this kind of intervention so soon after HTx. How would the HIT program work out with the *de novo* HTx recipients? Would they tolerate the exercise? How would it be to run the HIT program in such a decentralized way?

The planning, the years of completion, and the published results of the HITTS study have built a path of new insights of the exercise-based rehabilitation program from the early state to the long-term state after HTx. My thesis will hopefully give you some new knowledge about exercise after HTx. However, I am still curious about how to further extend the path in this field; there are still many unexplored hypotheses.

Oslo, February 2021

Katrine Rolid

Articles in the thesis

Paper 1

Rolid K, Andreassen AK, Yardley M, Bjørkelund E, Karason K, Wigh JP, Dall CH, Gustafsson F, Gullestad L, Nytrøen K. Clinical features and determinants of VO_{2peak} in *de novo* heart transplant recipients. *World J Transplant*. 2018 Sep 10; 8(5):188-197. doi: 10.5500/wjt.v8.i5.188.

Paper 2

Nytrøen K*, Rolid K*, Andreassen AK, Yardley M, Gude E, Dahle DO, Bjørkelund E, Relbo Authen A, Grov I, Philip Wigh J, Have Dall C, Gustafsson F, Karason K, Gullestad L. Effect of High-Intensity Interval Training in De Novo Heart Transplant Recipients in Scandinavia. One-Year Follow-Up of the HITTS Randomized, Controlled Study. *Circulation*. 2019 May 7; 139(19):2198-2211. doi: 10.1161/CIRCULATIONAHA.118.036747. Erratum in: *Circulation*. 2019 Oct 22; 140(17):e737.

*Contributed equally to the paper

Paper 3

Rolid K, Andreassen AK, Yardley M, Gude E, Bjørkelund E, Authen AR, Grov I, Pettersen KI, Dall CH, Karason K, Broch K, Gullestad L, Nytrøen K. High-intensity interval training and health-related quality of life in *de novo* heart transplant recipients – results from a randomized controlled trial. *Health Qual Life Outcomes*. 2020 Aug 17; 18(1):283. doi: 10.1186/s12955-020-01536-4.

Paper 4

Rolid K, Andreassen AK, Yardley M, Gude E, Bjørkelund E, Authen AR, Grov I, Broch K, Gullestad L, Nytrøen K. Long-term effects of high-intensity training vs moderate intensity training in heart transplant recipients: A 3-year follow-up study of the randomized-controlled HITTS study. *Am J Transplant*. 2020 Dec; 20(12):3538-3549.doi: 10.1111/ajt.16087. Epub 2020 Jun 28.

Errata Paper 1, Paper 2 and Paper 4

In Paper 1, and in supplementary Table 7 in Paper 2, the confidence intervals correspond to the unstandardized regression coefficient and not to the standardized regression coefficient as reported. In supplementary Table 7, Paper 2, reports an incorrect calculation for the mean difference variable of the dependent variable $\text{VO}_{2\text{peak}}$ (L/min), the correct calculation is $\text{VO}_{2\text{peak}} = \text{post-value} - \text{pre-value}$. These corrections to supplementary Table 7 have been published online.

In Paper 4, Table 3, the *(asterisk footnote) behind the standard deviation of the visual analogue scale score (high-intensity interval training group) is wrong and should be replaced with the ^c (footnote).

1 Introduction

1.1 The history of exercise-based rehabilitation after heart transplantation

The first human heart transplantation (HTx) was performed in December in 1967, and from an experimental procedure, it developed into an established therapy method for patients with end stage heart failure (1). Since the first HTx in Norway in 1983 (2), 1021 patients have received a HTx at Oslo University Hospital, Rikshospitalet by January 2021. Median survival worldwide after HTx is 10.8 years for adults, and for transplantations performed after 2002, the median survival is greater than 12 years, according to the International Society for Heart and Lung Transplantation (ISHLT) registry (3). Better surgical procedures and modern immunotherapies have contributed to the improved survival rates, and focus on post-operative care for a HTx recipient has shifted to the question of how to improve the long-term survival and quality of life (1).

A close association between exercise capacity and survival after HTx has been documented (4, 5) and exercise-based cardiac rehabilitation is recommended after HTx (6-12). Over the four last decades, cardiac rehabilitation exercise interventions have changed from non-standardized exercise protocols to more standardized exercise protocols with moderate intensity as the common prescription (7). High-intensity interval-based training (HIT) exercise protocols have been proven to be efficient in research studies (7, 13, 14), but HIT is still not implemented as standard therapy in clinical practice (11).

To the best of my knowledge, the first documented study of cardiac rehabilitation after HTx was in 1976 with a paper in Journal of American Medical Association (JAMA) by Christopherson et al. (15) from Stanford University Medical Center. The authors described the rehabilitation status of 56 HTx recipients six months after surgery. The participants in this study were educated in different lifestyle habits before being discharged from the hospital,

including unsupervised “moderate, regular physical exercise” and 91% of the participants were satisfyingly rehabilitated. The first publication to more specifically prescribe an early supervised outpatient exercise-based cardiac rehabilitation program was given in a case report by Squires et al. (16) in 1983. This paper showed the feasibility of an exercise program consisting of continuous aerobic exercise with moderate intensity (rated perceived exertion (RPE) of 12-13 according to the Borg scale (17)). The first larger exercise study (n = 62) was published in 1988 by Niset et al. (18), and it demonstrated that there were significant effects of an endurance exercise training program (intensity of 30–50% of working capacity) starting one month after HTx. The same year, Kavanagh et al. (19) was the first to report the effect of long-term endurance training on exercise capacity in 36 male HTx recipients starting 2 to 23 months after the transplantation. The exercise protocol in this study was prescribed walking 1.6 km five times per week with an intensity of 60%–70% of oxygen consumption (Borg scale 14). The first randomized controlled exercise trial was published in 1999 by Kobashigawa et al. (20). The participants were randomized to either a structured exercise program or to an unstructured home-based exercise program starting two weeks after the HTx. The structured exercise program consisted of strength training and aerobic exercises with moderate continuous training for at least 30 minutes 1–3 times per week over six months. Studies published from the middle of the 1970s to the end of the 1990s were similar in that the recommended or tested exercise intensity was moderate and continuous.

In 2009 a new approach to exercise after HTx was introduced when Haykowsky et al. (21) tested a combined exercise program of moderate intensity and high-intensity interval training (HIT) versus a control group (usual activities of daily living) in a randomized controlled trial. A few years later, Hermann et al. (22) and Nytrøen et al. (23) published randomized controlled trials of HIT versus a control group with no supervised exercise in maintenance HTx recipients. In these studies, HIT was demonstrated to be safe and more effective than the

non-exercising control group > 1 year after the HTx (24). The novelty of the study by Nytrøen et al. (23) was that follow-up to the HIT was decentralized, while Hermann et al. (22) performed an in-hospital HIT intervention. In 2017, Yardley et al. (25) was the first to report the long-term effects of HIT in a 5-year follow-up study of maintenance HTx recipients, showing superior effects of HIT on symptoms of anxiety compared to a control group that had no specific exercise. However, the effect of HIT versus moderate intensity continuous training (MICT) was poorly understood. In 2014, a crossover trial by Dall et al. (26) showed that HIT was superior to MICT in maintenance HTx recipients. A historical timeline of novel studies involving exercise from 1976–2020 is given in Figure 1.

In a recent updated position paper from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology, it is stated that HIT is safe and effective after HTx, and that the restrictions placed on HTx recipients with regard to exercise do not seem to rely on evidence-based knowledge. The time has come to update the exercise recommendations in the HTx population (11).

The effect of HIT versus MICT in *de novo* HTx recipients is however still unknown (6, 7).

The main goal of this thesis is to investigate the effect of HIT versus MICT in *de novo* heart transplant recipients with short- and long-term follow-up.

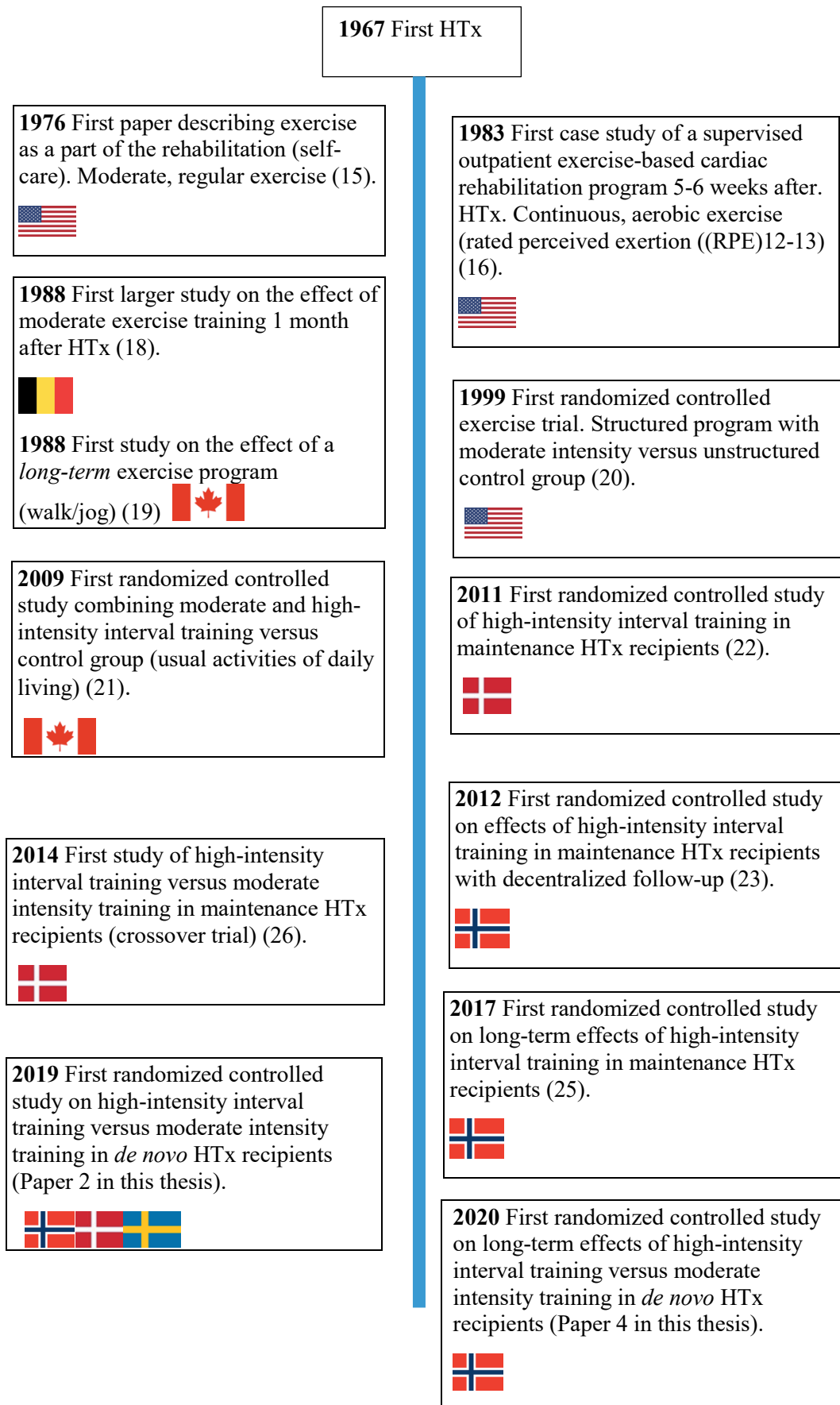


Figure 1 Historical timeline over novelty studies involving exercise after HTx from 1976-2020.

1.2 Physical activity versus exercise

The terms physical activity and exercise are often used interchangeably. However, there is a difference between these terms that needs to be clarified. *“Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure”*, (27, p. 126) while *“exercise is a subset of physical activity that is planned, structured, and repetitive, and has as a final or an intermediate objective the improvement or maintenance of physical fitness”* (27, p. 126). In this thesis, it is useful to distinguish between these two terms, since each of these two specific exercise interventions and measuring of physical activity will be reported.

1.3 Peak oxygen consumption versus maximal oxygen consumption

Peak oxygen consumption ($VO_{2\text{peak}}$) is the preferred method for measuring exercise capacity and cardiovascular fitness (28). In patient populations, $VO_{2\text{peak}}$ is the highest oxygen uptake recorded during exercise (28, 29). The term $VO_{2\text{peak}}$ is used instead of $VO_{2\text{max}}$ because most patients are not able to achieve a $VO_{2\text{max}}$, which is defined as a failure of VO_2 to increase despite increasing work effort (30). The importance of evaluating $VO_{2\text{peak}}$ has been stated in several scientific statements both in the US and Europe (29, 31, 32).

HTx recipients have a reduced $VO_{2\text{peak}}$ compared to an age- and gender-adjusted healthy population (6, 7).

1.4 High-intensity interval training (HIT) versus moderate intensity continuous training (MICT)

HIT can be performed in different ways from sprint-interval (low volume, supramaximal exercise training) to high-intensity aerobic exercise training bouts with an intensity between

85–95% of peak effort (85–95% of peak heart rate or 80–90% of VO_{2peak} or rated perceived exertion (RPE) of 16–18 on the Borg scale (33, 34)). No versatile model of how to perform HIT in a clinical setting exists. An often-used HIT model in cardiac rehabilitation and cardiac exercise research is the 4 x 4 min model originally developed for soccer players in Trondheim (Norway) (35). This model consists of four high-intensity interval bouts (85–95% of peak effort) of a duration of four minutes, with an active recovery period of three minutes between the interval bouts (33, 34, 36-38). In contrast, MICT is continuous exercise with an intensity of 60–80% of peak effort with a duration of 30 minutes (34).

HIT is an effective form of exercise and is shown to increase VO_{2peak} more than MICT in various patient populations as well as in healthy populations (33, 39). In the HTx population, to date only one small cross-over study has compared HIT versus MICT in maintenance HTx recipients (26). In the study by Dall et al. (26), 16 HTx recipients (mean 6.5 years after HTx) were randomized to either HIT or MICT in a 12-week supervised intervention period. The wash-out period (a period with no exercise intervention /normal lifestyle) was five months. Both groups had significant improvement in VO_{2peak} , but with a significantly higher improvement in the HIT group.

1.5 The *de novo* heart transplant and exercise

The newly transplanted heart is without nerve supply, since both the sympathetic and the parasympathetic nerve fibers are cut during the surgical procedure of the donor heart (40).

The HTx recipient typically has an elevated resting heart rate due to this absence of parasympathetic nerves. During exercise, heart rate response is delayed because the heart is depending on circulating catecholamines to respond appropriately to stress (40). In practice, what is seen is a slow increase in heart rate at the beginning of an exercise session, and after the exercise is stopped, the heart rate usually continues to increase for a few minutes (40).

This pattern is the heart rate response typically seen with exercise in the early phase after HTx (41, 42). A significantly improved, and near to normal, heart rate response during exercise the first year after HTx has been shown (41), and there is evidence that cardiac reinnervation subsequently occurs (42, 43). Studies have documented sympathetic reinnervation 5–6 months after HTx and parasympathetic reinnervation 1–3 years post HTx (42).

1.6 Resistance exercise training after heart transplantation

The importance of resistance exercise training after HTx is multifactorial and has effects both on skeletal muscle function and on bone mineral density (44, 45).

Skeletal muscles in HTx recipients have been shown to be altered both in function and in structure. These alterations are due to the use of corticosteroids and cyclosporine, as well as pre-transplant muscular abnormalities that are often observed in chronic heart failure patients (46).

Studies with biopsies taken from the vastus lateralis muscle at different times after HTx have found decreased capillary density between 1–12 months post-transplantation (45, 47, 48), which might be a result of persistent reduced capillary density pre-transplant (47). Long-term use of corticosteroids and cyclosporine damages the microvasculature in the muscle cells, which also has detrimental effects on the capillarization (45).

The first evidence of the effect of resistance exercise therapy on corticosteroid myopathy was reported in a small study of renal participants in 1985 (49). Ten years later, Braith et al. (50) demonstrated that resistance training (versus no resistance training) had a significant effect on knee extensor strength, upper-body strength and fat-free mass in a small, controlled study with HTx recipients. The possible effects of resistance training on corticosteroid myopathy after HTx was substantiated in a study where muscle biopsies from vastus lateralis were taken

before and after a resistance training program. The resistance exercise training group had a shift from the less oxidative muscular fiber type II to the more oxidative muscular fiber type I (51).

Osteoporosis is a known comorbidity after HTx due to the negative effects of glucocorticoids on bone mineral density (52), and other pre-transplant factors like physical inactivity, weight loss, poor nutrition, impaired gonadal function and medications can also have deleterious effects on the skeleton (53). Resistance exercise training after HTx is an effective method for restoring bone loss after HTx (54).

1.7 Hemodynamic responses to exercise after heart transplantation

HTx recipients have a lower end-diastolic volume (45, 55, 56), lower stroke volume, and a higher pulmonary capillary wedge pressure (45, 55) both at rest and at peak exercise compared to an age- and gender-adjusted healthy population. Possible mechanisms behind these diminished cardiac functions are explained by the decreased adrenergic tone due to the denervated heart, ischemic injury related to the transplant surgery procedure, or cardiac hypertrophy because of cyclosporine-induced arterial pressure (45, 56).

1.8 Arteriovenous oxygen difference and exercise

Arteriovenous oxygen difference (a-vO₂ diff) is an important determinant of VO_{2peak} (57). A-vO₂ diff can be calculated by the Fick equation (58): cardiac output = oxygen consumption/ a-vO₂ diff. The specifically relevance to exercise is that the Fick equation states that the maximal cardiac output equals the amount of maximal VO_{2peak} divided by the amount of extracted oxygen from the blood of the working muscles (57). Maximal a-vO₂ diff has been shown to be lower in HTx recipients than in healthy controls (55, 59). The diminished a-vO₂

diff observed in HTx recipients is explained by a peripheral abnormality in oxygen extraction and/or oxygen utilization (45, 55).

1.9 Endothelial function and exercise

Endothelial dysfunction is associated with cardiovascular-related events and death after HTx (60), and is a predictor of cardiac allograft vasculopathy (CAV) (61). CAV is a special form of coronary atherosclerosis after HTx. The disease is described as a thickening of both the intima of the epicardial and intramyocardial arteries of the graft (62).

In a recent systematic review and meta-analysis of the effect of exercise in HTx recipients, the claim that exercise increases endothelial function could not be supported because there are very few high-quality studies (63). However, in one study comparing HIT versus a control group without exercise, endothelial function increased significantly in the HIT group (22), suggesting the effect of exercise on HIT is dependent upon intensity (favorable effects of intensity > 80% of VO_{2peak}) (63).

1.10 Long-term effects of exercise after heart transplantation

An increased VO_{2peak} is associated with long-term survival after HTx (4). There are few randomized controlled studies on the long-term effects of exercise after HTx (6), and only one on the long-term effects of HIT (25). The 5-year follow-up of the TEX (Transplant EXercise study) (23) from our research group found no difference in VO_{2peak} between HIT and the control group five years after the intervention. However, the HIT group reported reduced symptoms of anxiety (25).

One small observational study on the long-term effects of exercise interventions 12 years after HTx showed that VO_{2peak} decreases with time, but not more than what is expected with age (64).

1.11 Physical activity after heart transplantation

One of the goals after an organ transplantation is to achieve and maintain good lifestyle habits, and one of these habits is daily physical activity (65). In studies measuring daily physical activity in HTx recipients, some report low levels of daily physical activity (66-69), while other show moderate to high levels of physical activity > 1 year after HTx (25, 70, 71). A study of different organ transplant recipients found that barriers to being physically active were things like costs of fitness centers, insufficient exercise guidelines, and the feeling of having less strength post-transplant. Facilitators for physical activity were feeling healthy when performing activity, motivation, social support, knowledge, and confidence in physician-recommended exercise (72).

1.12 A decentralized cardiac rehabilitation model

Exercise-based cardiac rehabilitation is performed with different models (73, 74). The most frequently used is the supervised center-based model with exercise performed either in-hospital or in rehabilitation centers. Home-based cardiac rehabilitation programs are cardiac rehabilitation that are performed at home (either supervised or unsupervised) or can be located in a non-clinical setting (community centers, health clubs) (6, 75). These home-based programs might be better than the center-based programs in terms of flexibility and patients compliance (75). Home-based exercise programs with moderate intensity are reported to be effective and safe in the HTx population (76-78). Nytrøen et al. (23) was the first to report

results from a decentralized HIT-model in HTx recipients. The participants performed HIT in their local communities near their home, with 1:1 supervision from local physical therapists. This model was found to be both safe and effective in maintenance HTx recipients.

1.13 Health-related quality of life

Because survival rates after HTx have increased so much, quality of life (QoL) has become an important outcome measure in care of HTx recipients (79, 80). QoL and health related quality of life (HRQoL) are often used interchangeably, and distinguishing between the two may be problematic (81). When measuring QoL in a medical setting, we are often interested in the aspects of QoL that relate to a person's health, and therefore the term HRQoL is often more suitable (82). HRQoL is a multidimensional concept including domains like physical function, role function, social function, general health, and mental health (82).

Although the HTx patients live longer, medical complications affecting the patients HRQoL may occur in both the short- and long-term after the transplantation. Infections and graft loss are the most feared complications in the early phase after HTx. Cancer, renal failure, CAV and diabetes are conditions seen in the later phases (83). These medical complications and conditions are mainly related to side-effects of life-long immunosuppression (83). For these reasons, one of the main goals after HTx is to improve HRQoL.

A newly-published (2020) systematic review of HRQoL in adult HTx recipients highlights the stability of HRQoL up to ten years after HTx and concludes that HRQoL is influenced by different factors such as physical factors (pain, gastrointestinal symptoms, sexual dysfunction), psychological factors (depression), and sociodemographic factors (social, environmental, age and gender) (84). Prior to HTx, HRQoL is often greatly impaired in this population due to the severity of heart failure (79, 84, 85). Longitudinal studies have reported

that HRQoL post-HTx improves significantly over the pre-HTx HRQoL measures, with the greatest improvements occurring during the first six (85) and seven months (86). Most studies reporting HRQoL in the long-term after HTx have shown stable and good HRQoL up to five (85, 87), ten (88) and as long as up to 20 (89) years after HTx.

Both the physical domains of HRQoL and exercise capacities in the HTx population are reported to be lower than the general population (6, 7) and thus, the domain of physical function in HRQoL is of particular interest. The physical function subscale in Short-Form-36 (SF-36) has been related to peak oxygen consumption (VO_{2peak}) in different studies (5, 90), reflecting an association between self-reported physical function and objective measurements. The impact of exercise capacity on HRQoL has been studied at different times after HTx (4, 23, 25, 76, 90-100), and a summary of these studies is presented in Table 1.

Table 1 Review of studies with HRQoL and physical function outcomes.

Study	Design N	Time after HTx Median (IR) Mean \pm SD	Questionnaire	Physical function Outcome, measurement	Main results
Evangelista et al. (2004) (99)	HTx versus HTx candidates N= 50 (HTx females only) N= 50 HTx candidates	5.2 \pm 4.4 yrs.	MLHFQ, BDI CAS	6 MWT	MLHFQ scores (total, physical and emotional): HTx vs HTx candidates \downarrow Depression: HTx \downarrow vs HTx candidates Perceived control (CAS): HTx \uparrow vs HTx candidates Correlation between 6 MWT and physical health subscale (HRQoL)
Ulubay et al. (2007) (95)	Prospective study Pre HTx (n= 7) Post HTx (n= 7) Healthy con. (n= 14)	10–28 mos.	SF-36, BDI	VO _{2peak} , bicycle	VO _{2peak} : Healthy con. \uparrow vs HTx and pre-HTx VO _{2peak} : Healthy con. \uparrow vs pre HTx RP, GH, MH: HTx \uparrow vs pre HTx Symptoms of depression: HTx \downarrow versus pre-HTx In all three groups: sig. correlation between VO _{2peak} and VT, VO _{2peak} and GH and VO _{2peak} and depression
Karapolat et al. (2007) (98)	RCT, hospital-based ex. versus home-based ex. 8 wks. follow-up N = 38	Hospital ex.: 14.5 \pm 17.21 mos. Home-based ex.: 16.69 \pm 17.64 mos.	SF-36, STAI BDI	VO _{2peak}	VO _{2peak} : Hospital-based ex. vs home based ex. \uparrow PF, RP, BP, GH, RE, MH: Hospital ex. \uparrow BP: home-based ex. \uparrow

Karapolat et al. (2007) (96)	Cross-sectional N = 34	19.3 ± 12.61 mos.	SF-36, BDI, STAI	VO _{2peak} , treadmill	Sig. correlation between VO _{2peak} and depression score and anxiety Significant association between PF and VO _{2peak}
Karapolat et al. (2008) (90)	Cross-sectional N = 31	21.90 ± 22.70 mos.	SF-36	VO _{2peak} , treadmill	Sig. correlation between VO _{2peak} and PF and VO _{2peak} and RP
Wu et al. (2008) (76)	RCT, Home-based ex. versus con. (no ex.), 8 wks. follow-up N = 37	Ex.:18.6 ± 21.0 mos. Con.:31.4 ± 23.0 mos.	WHOQOL- BREF	VO _{2peak} , bicycle, Muscle strength (lower limbs)	QoL (physical domain): Ex. ↑
Buendia et al. (2011) (100)	Prospective Longitudinal N= 58	2 , 6, 12 and 24 mos.	EQ-5 D	METs and time of ex., treadmill	METs ↑ EQ-5D ↑
Hsu et al. (2011) (93)	Clinical trial (non- randomized) HTx versus CABG surgery, 12 wks. follow- up HTx (n=45) CABG (n=34)	HTx: 70 ± 33 days CABG: 36 ± 18	SF-36	VO _{2peak} , Bicycle	VO _{2peak} : Both groups ↑ PCS: Both groups ↑ PF, RP, BP, SF, RE, MH: HTx ↑ PF, RP, BP, SF: CABG ↑
Christensen et al. (2012) (92)	RCT, HIT versus con., 8 wks. follow-up N= 27	HIT: 6.8 ±4.0 yr. Con: 7.0 ± 5.5yr	SF-36 version 1 HADS	VO _{2peak} , Bicycle	VO _{2peak} : HIT ↑ Self-perceived health: HIT ↑ Symptoms of anxiety and depression: HIT ↓
Nytrøen et al. (2012) (23)	RCT, HIT versus con. (no exercise), 1- year follow-up N= 48	4.1 ± 2.2 yr.	SF-36v2	VO _{2peak} , treadmill	VO _{2peak} : HIT ↑ versus con. HRQL (GH): HIT ↑

Imamura et al. (2015) (97)	Longitudinal N= 21	6, 12 and 24 mos.	MLHFQ	VO _{2peak} HRV Bicycle	Significant correlations between heart rate recovery and MLHFQ scores
Dall et al. (2015) (91)	RCT (crossover), HIT versus MICT, 12 wks. follow-up	Mean (range) 6.4 (1-17) yrs. N=16	SF-36v1 HADS	VO _{2peak} , bicycle	VO _{2peak} : HIT ↑ vs con. PCS: HIT ↑ Depression: HIT ↓ Anxiety: Both groups ↓
Yardley et al. (2016) (4)	Retrospective, observational, N= 303	CPET cohort inclusion: 3(6) yrs. SF-36 cohort inclusion: 5 (6) yrs.	SF-36v1	VO _{2peak} , bicycle	VO _{2peak} and self-reported physical function were strong predictors for long-term survival after HTx.
Yardley et al. (2017) (25)	5 yrs. follow-up after HTx HIT versus con. (no intervention) N = 41	4.1 ± 2.2 yr. (at inclusion)	SF-36 BDI HADS	VO _{2peak} , treadmill	RP: HIT ↑ Anxiety: HIT ↓ vs con.

↑ = Significant increase; ↓ = Significant decrease

Abbreviations: BDI, Becks Depression Inventory; CABG; Coronary Artery Bypass Grafting; CAS, Control Attitude Scale; con., control; CPET, cardiopulmonary exercise test; EQ-5D, Euroqol-5D; ex., exercise; HADS, Hospital Anxiety and Depression Scale; HIT, High-intensity Interval Training; HRQoL, health-related quality of life; HTx, heart transplantation; METs, metabolic equivalents, MLHFQ, Minnesota Living with Heart Failure; mos., months; 6 MWT, 6 minute walking test; RCT, randomized controlled trial; SF-36, Short form-36; STAI, Stait-Track Anxiety Inventory; wks., weeks; WHOQOL-BREF, brief version of the World Health Organization Questionnaire on Quality of Life.

1.14 Symptoms of depression and anxiety

A prevailing depressive mood disorder is reported to occur in up to 63% of patients in the first years after HTx, while up to 25% display anxiety-related disorders (101). Furthermore, the risk of episodes of depressive and anxiety conditions is thought to be higher the first year after HTx than in subsequent post-transplant years (101).

Depression is associated with mortality after HTx (102-104). Hence, an evaluation of the HTx recipients' mental health status is important for determining those who are at risk for developing mental health problems, and a need for non-pharmacological interventions for improving mental health in HTx recipients has been stated (80, 105). Exercise-based cardiac rehabilitation is one of the interventions that has promising results (105).

Studies in maintenance HTx recipients have shown that exercise reduces symptoms of depression and anxiety after just eight weeks of physical exercise compared to no exercise (91, 92). Long-term effects of exercise on symptoms of anxiety have also been demonstrated in a five-year follow-up in one of our previous studies (25).

2 Main aims of the study

- 1.** To investigate the clinical features and predictors of $VO_{2\text{peak}}$ in *de novo* HTx recipients.
- 2.** To compare the effects of HIT versus MICT on the exercise capacities of *de novo* HTx recipients with a 1-year follow-up.
- 3.** To compare the effects of HIT versus MICT on health-related quality of life in *de novo* HTx recipients.
- 4.** To compare the long-term effects of HIT versus MICT on exercise capacity in *de novo* HTx recipients.

3 Materials and methods

3.1 Study design

All four papers in this thesis are based on the randomized controlled HITTS (High-intensity Interval Training in De Novo Heart Transplant Recipients in Scandinavia) trial with 1-year and 3-year follow-ups. A design paper of the study was previously published (106). A study overview including the study design and which parts of the study the papers included in this thesis belong to is shown in Figure 2.

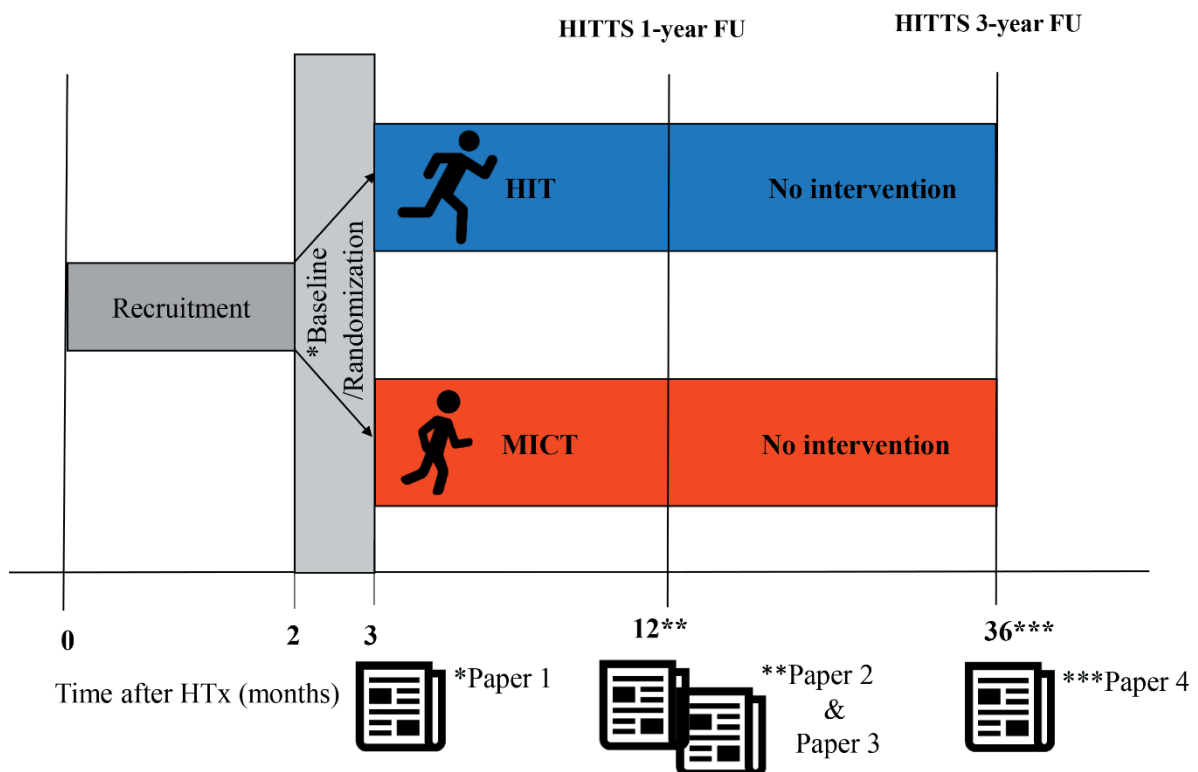


Figure 2 Design of the HITTS trial and papers in this thesis.

3.2 The heart transplant cohort in the HITTS study

The three first papers are based on the entire cohort from the HITTS trial lasting from 2013–2017 (106). All new HTx recipients at Oslo University Hospital, Rikshospitalet, Norway,

Sahlgrenska University Hospital, Gothenburg, Sweden, and Copenhagen University Hospital, Rigshospitalet, Denmark, were assessed for eligibility.

Inclusion criteria: Medical stable HTx patients; > 18 years old; receiving immunosuppressive treatment according to local protocols; motivated for participating in a 9-month long exercise intervention. Participants were also assessed for ongoing rejections. According to standardization of nomenclature in the diagnosis of heart rejections stated in the consensus report by the International Society of Heart and Lung Transplantation (ISHLT) (2005) (107), a grade 1 R = mild rejection; grade 2 R = moderate rejection; grade 3R = severe rejection. In case of rejections, inclusion was withheld until one clean biopsy was present after a rejection grade 1 R and two clean biopsies after a rejection grade 2 R. A rejection grade 3 was an exclusion criteria.

Of the 155 HTx recipients eligible for inclusion, 83 were randomized to either HIT or MICT and 72 were excluded. Reasons for exclusion were: Not meeting the inclusion criteria; cognitive issues (n=4), physical disabilities (n=3), medical complications (n=3), contagion (n=3), no physical therapist available (n=5), lack of motivation for participation (n=15), logistics reasons (n=14), and multiorgan transplantation (n=2). Two participants were excluded after randomization but before baseline testing because of medical complications (n=1) and withdrawal (n=1). In total, 81 participants, 39 in the HIT group and 42 in the MICT group, were initially included in the study. At the 1-year follow-up study, these numbers had decreased slightly to 78 total participants, 37 in HIT and 41 in MICT. The two dropouts in the HIT group were due to hospitalization due to nose-and throat related issues (n=1) and non-compliance with the exercise protocol (n=1). The single drop-out in the MICT group was because of a brain arteriovenous malformation.

A flow-chart of enrollment in the HITTS study is shown in Figure 3**.

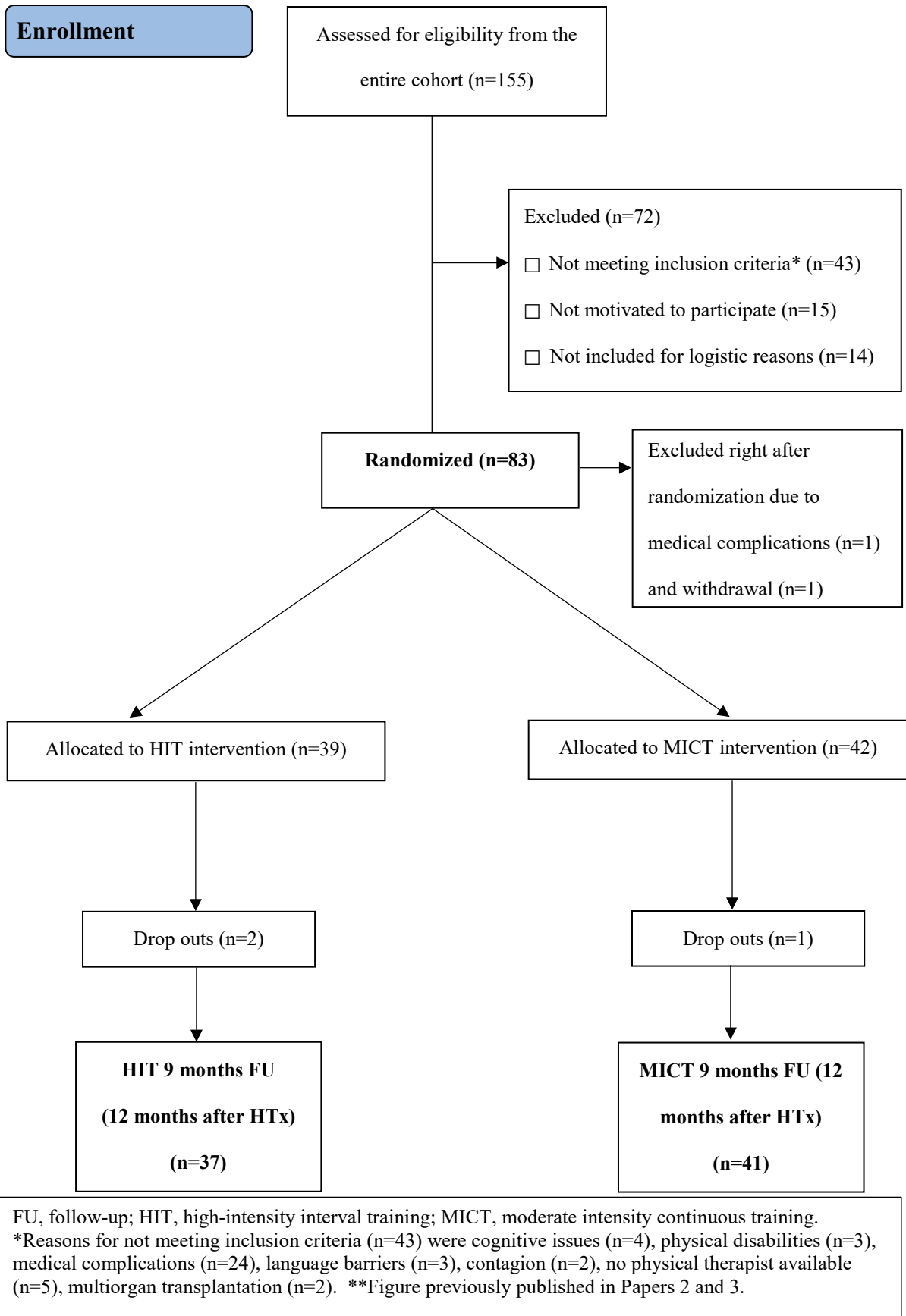


Figure 3 Patient recruitment and follow-up.

3.3 Timeline of methods and follow-up in the HITTS study

An overview of the different methods used in the HITTS study at 1-year and 3-year follow-ups is in Table 2.

Table 2 Timeline over the methods in the HITTS study described in this thesis*.

	Before inclusion	After inclusion, time after HTx			
		Mean 11 (range 7-16) wks.	6 mos.	12 mos.	36 mos.
Informed consent	x				x
Physical examination	x	x	x	x	x
VO _{2peak} (CPET)		x		x	x
Right heart catheterization		x		x	
Isokinetic muscle strength		x		x	x
BIA		x		x	x
Echocardiography		x		x	x
24 h blood pressure		x		x	x
Routine lab test	x	x	x	x	x
Endothelial function		x		x	
HRQoL		x		x	x
Tolerability, safety, adverse events /severe adverse events		x	x	x	x
Activity monitor					x
Physical activity questionnaire					x

BIA, bioelectrical impedance analysis; CPET, cardiopulmonary exercise test; HRQoL, health-related quality of life. *There are other secondary endpoints in the HITTS study (106) that are not captured in this thesis.

The participants and local physical therapists were in contact with the in-hospital physical therapists (HITTS collaborators at each study site) at different time points during the intervention period in the HITTS 1-year follow-up study (Table 3). At the main center in Norway, the author of this thesis was the responsible physical therapist and she also cooperated with the responsible in-hospital physical therapists in Gothenburg and Copenhagen.

Table 3 Timeline over the contact with local physical therapists / follow-up of the exercise interventions (both HIT and MICT).

	Before inclusion	After inclusion, time after HTx			
		Mean 11 (range 7-16) wks.	6 mos.	9 mos.	12 mos.
Initial contact between in-hospital physical therapist and the local physical therapist	x				
Pre-planned contact by phone call from in-hospital physical therapist to the local physical therapist		x	x	x	x
Delivery of exercise log from local physical therapist to the in-hospital physical therapist			x	x	x
Pre-planned face-to-face contact between study participant and in-hospital physical therapist		x	x		x

3.4 HITTS 3-year follow-up

The HITTS 3-year follow-up study (Paper 4) was an extension of the HITTS 1-year follow-up study of the Norwegian cohort. Participants in Norway who completed the HITTS 1-year follow-up were invited to participate in the 3-year follow-up study. Of the original 71

Norwegian participants who completed the 1-year study, 65 participants were entered into the 3-year follow-up study; of these, 62 of these participants completed this follow-up. Of the original 34 Norwegian participants allocated to the HIT group, two participants withdrew, one declined further participation, one was excluded due to psychiatric issues, and two died (1 legionella pneumonia and 1 renal cancer), leaving 28 participants from the original HIT group. Of the original 37 Norwegian participants allocated to the MICT group, reasons for loss to the follow-up were severe graft-failure (on HTx waiting list) and two deaths (1 infection, and 1 graft-failure due to early CAV), which left 34 participants from the original MICT group. A flow-chart showing the enrollment in the HITTS 3-year follow-up study is published in Paper 4.

3.5 Randomization

A randomization list was generated by a third party using random permuted blocks through a computer algorithm and a pseudorandom number generator. The treatment allocation (HIT or MICT) was stored in sealed and numbered envelopes. Participants were given a randomization number at inclusion, and the numbered envelopes were not opened until after the baseline cardiopulmonary exercise test (CPET).

3.6 General lifestyle advice

Participants in both groups were given general lifestyle advice at time of inclusion and during follow-up. Participants were advised about how to prevent infections as well as to eat a healthy diet, get regular exercise, and not smoke.

3.7 Exercise interventions

Before leaving the hospital, participants in both groups were given an extensive educational lesson by the in-hospital physical therapist (HITTS collaborator) about how to practice the intervention.

Both exercise interventions were carried out in the participants' local communities and participants in both groups were followed up individually by a physical therapist 2–3 times per week for nine months. The interventions were driven by the decentralized rehabilitation model with close cooperation between the local physical therapists and the in-hospital physical therapist (Figure 4). The intervention periods were divided in three periods, each lasting for approximately three months. The local physical therapists received both oral and written information about HIT or MICT, including standardized exercise logs for each intervention prior to the first exercise session. The local physical therapists were responsible for collecting data for the exercise logs and mailing them to the in-hospital physical therapist (HITTS study collaborator) after each exercise period. The local physical therapists were instructed to keep copies of the logs before returning them. At the beginning of a new exercise period, the previous exercise period was discussed at the same session as the new period being planned. The in-hospital physical therapist (HITTS study collaborators) contacted the local physical therapists routinely four times during the intervention period at the following time points: before the first exercise session (approximately three months after HTx), after the first exercise period (six months after HTx), after the second exercise period (nine months after HTx), and after the third exercise period (12 months after HTx).

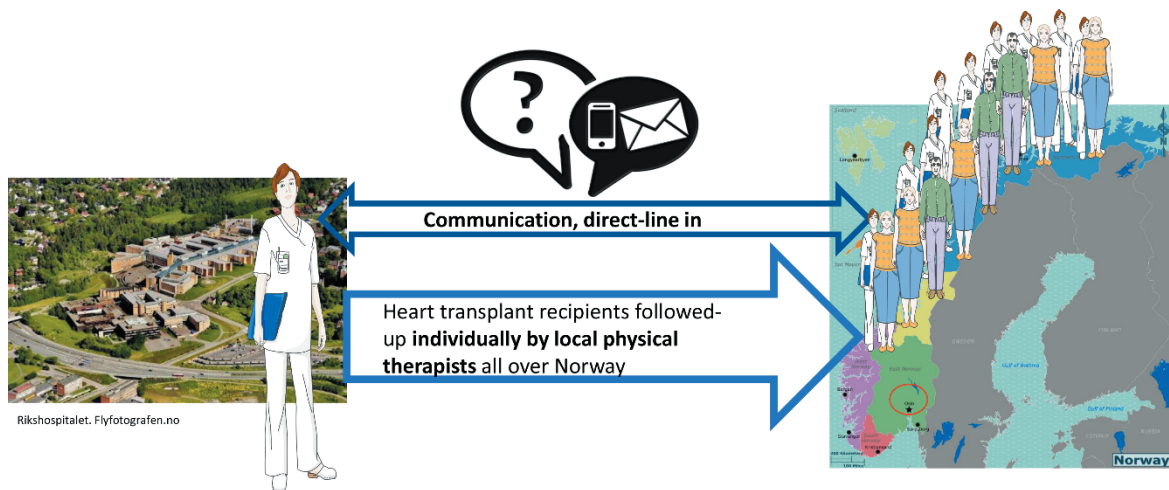


Figure 4 Illustration of the decentralized rehabilitation model in Norway.

3.7.1 High-intensity interval training (HIT)

The HIT intervention was based on the 4 x 4 model (described in Chapter 1.4) which has been used in several research studies and is recommended for use in clinical practice (23, 33, 34, 36). To ensure tolerability for the HIT intervention, participants started out with a session of 1–2-minute interval bouts in two series with an intensity of 85–95% of peak effort. In the first intervention period (3–6 months after HTx), the participants had one resistance training session and one combined session (HIT and resistance training). The second intervention period (6–9 months after HTx) consisted of two HIT sessions and one resistance training session (supervised or non-supervised). In the third intervention period (9–12 months after HTx), the participants were supposed to have performed three HIT sessions per week. The duration of the interval bouts and/or the number of the sessions were gradually increased throughout the intervention periods. The main goal was that a participant should be able to perform four 4-min interval bouts during the last (third) intervention period. A warm-up period of 10 minutes and a cool down period of at least 5 minutes was an important part of

every HIT session (Figure 5).

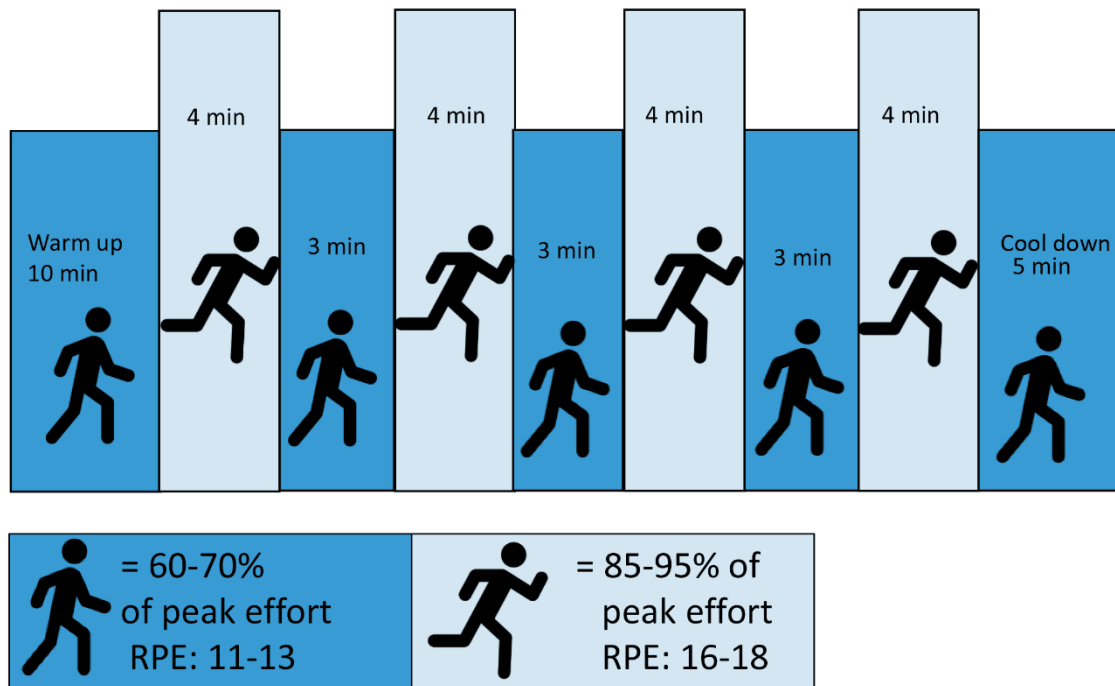


Figure 5 Illustration of the high-intensity training protocol.

3.7.2 Moderate continuous intensity training (MICT)

The MICT intervention consisted of approximately 25 minutes of exercise at < 80% of peak effort with a warm-up period of 10 minutes and a cool-down period of 5 minutes (total duration 40 minutes) (Figure 6). In addition, the participants performed resistance training. The goal was to have a progression in the exercise program during the three intervention periods.

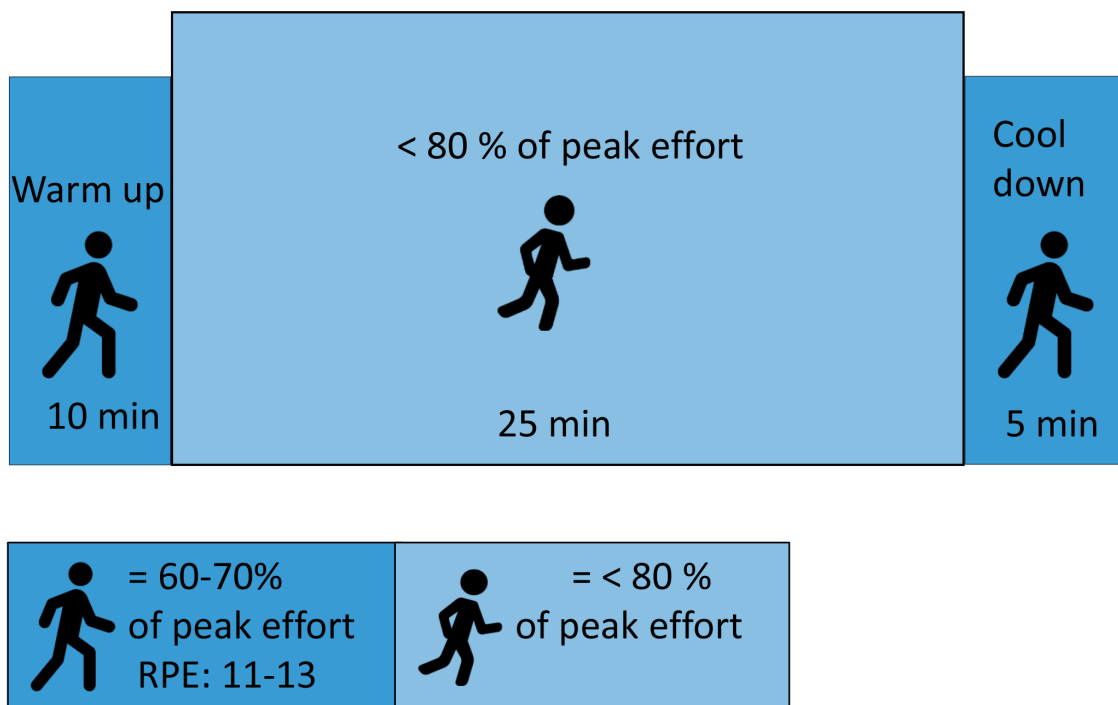


Figure 6 Illustration of the moderate intensity continuous training protocol.

3.8 Strength training and stretching exercises

Participants in both groups performed strength training, consisting of general strength training for the large muscle groups in the upper body and the lower limbs. For the upper body, only light exercises such as biceps curls and shoulder press with low weights, and core strength exercises for the abdominal and lumbar muscles were recommended. Heavier exercises were recommended for the lower limbs, and here the preferred exercises were squats, leg presses and calf raises. In addition, participants in both groups were recommended to do stretching exercises at the end of each training session.

3.9 Exercise monitoring and exercise logs

All supervised exercise sessions in both groups were logged and monitored with a heart rate monitor (Model Polar FT1 or Polar A300, Polar Electro Oy, Kempele, Finland). The exercise logs (Word paper format) were standardized for both groups.

For both groups, prespecified information from the baseline CPET were filled out at the study centers before starting the intervention, including date of CPET, VO_{2peak} (mL/kg/min), percent of predicted VO_{2peak} , maximal speed and maximal gradient at the treadmill (or watt if bicycle test), duration (minutes) and length (meters), heart rate (rest and maximal). Contact information for the study team was provided on the exercise logs.

Description of the HIT exercise log

In the page margins, a short, standardized description of the HIT protocol, and a recommendation of how to individualize and adjust the HIT sessions according to the participant's physical fitness, were prespecified. Date of each HIT session should be documented. The local physical therapists should register the heart rate before starting the exercise, at the end of the warm-up period, at the end of every interval bout, and after the cool-down period. At the last page of the exercise log, the physical therapists could write comments to the exercise period.

Description of the MICT exercise log

In the page margins, a short, standardized description of how the MICT exercise sessions could be performed and that the participants should not do interval training was prespecified. In the MICT exercise log, the local physical therapist should register the date, what kind of exercise activity were performed, average RPE according to the Borg scale (17) during the

exercise session, as well as the maximal heart rate and the average heart rate for the total exercise session. If they had any comments to the exercise period, these should be reported on the last page of the exercise log.

For both groups, the physical therapists were informed to register any adverse events during the exercise sessions and contact the project team whenever necessary.

3.10 Cardiopulmonary exercise testing

The CPET was performed predominantly on a treadmill (Woodway, PPS 55 Med-I, GmbH; Weil am Rhein, Germany) after an individualized ramp protocol (108) using the breath-by-breath method (Jaeger® Masterscreen® CPX, Carefusion; Hoechberg, Germany). The test protocol was an individualized protocol adapted from the Working Group on Cardiac Rehabilitation & Exercise Physiology and Working Group on Heart Failure of the European Society of Cardiology (108). The test was performed with a constant speed between 3–6 km/h chosen during the 10 minutes warm-up period and the incline of the treadmill was increased with 2% every second minute until exhaustion. Immediately after the test, participants were seated on a chair to measure the chronotropic responses. Heart rate was measured continuously by electrocardiogram (Cardiosoft), while blood pressure was measured every second minute (automatically by Tango+, SunTech, Medical Inc., Morrisville, NC, USA). The test was symptom limited. Criteria for an acceptable test were respiratory exchange ratio (RER) > 1.05 and/or RPE >18–19 (17). Lung function was measured by spirometry before starting the exercise test (before the warm-up period). Pictures from a treadmill test are shown in Figures 7–9. (All pictures are used with the consent of the participant.)



Figure 7 Picture of a study participant walking at the beginning of the exercise test.



Figure 8 Picture of a study participant at the end of the exercise test.

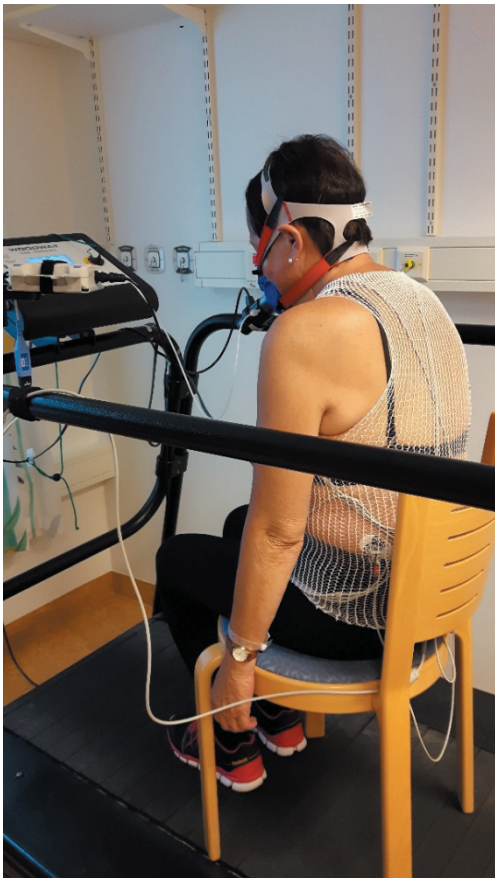


Figure 9 Picture of a study participant sitting at the end of the test, recovery period.

Variables calculated online were $VO_{2\text{peak}}$, O_2 pulse, maximum ventilation (VE) and RER. The anaerobic threshold (AT) was determined by the equivalent for oxygen (EqO_2) (25, 109) and automatically calculated from the CPET software. To measure the ventilator efficiency, the VE/ VCO_2 slope was estimated from the beginning of the exercise test to the AT (25).

Four of the Norwegian participants had orthopedic issues in the feet or back and could not walk on the treadmill. These participants were tested on bicycles (Schiller Cardiovit CS-200 Excellence, Baar, Switzerland). The author of this thesis performed (or was present at) all the exercise tests except for one in the HITTS 1-year follow-up. For the 3-year follow-up study, all the exercise tests were performed by the author.

Participants in Sweden and Denmark were tested on a bicycle as per clinical practice in those countries. The CPET equipment used in Sweden and Denmark were Jaeger®, Oxy Con Pro® and Jaeger® Vyntus® CPX, Intramedic, Gentofte, Denmark, respectively.

3.11 Muscle strength testing

Muscle strength in the hamstrings and quadriceps femoris was tested isokinetically with a dynamometer (Cybex 6000; Lumex, Ronkonkoma, NY, USA) (110) (Figure 10).

Participants warmed up with 5–10 minutes on a bicycle before the test, which was performed in a sitting position with the upper body fixed, and each leg was tested separately. Maximal muscle strength was performed with five repetitions on an angular velocity of 60 °/s. and individually mean peak values were calculated in Newton Meters. Thirty repetitions at 240 °/s were performed for the muscular exercise capacity. Total work in Joule (J) was calculated as the sum of all repetitions (111).



Figure 10 Isokinetic strength testing measurements, Cybex 6000.

Participants in Denmark and Sweden (HITTS 1-year follow-up study) were instructed to use the same test-protocol as described above, but the two centers used different isokinetic devices. The equipment used in Denmark was Kinetic Communicator (model 500-11, Chattanooga, TN, USA) (112) and in Sweden IsoMed2000 (D. & R. Ferstl GmbH, Germany) (113).

3.12 Test of endothelial function

Peripheral endothelial function was measured with brachial artery flow-mediated dilation (FMD) and peripheral arterial tonometry (PAT), which are two validated assessments (114).

Both FMD and PAT were measured in a fasting state in the morning before other clinical tests. FMD was assessed with an ultrasound probe (Zonare, Medical Systems, Mountain View, CA, USA) after 5 minutes of occlusion of the forearm. Peripheral arterial tone (PAT; EndoPAT 2000; Itamar Medical, Caesara, Israel) was recorded with a probe on the index-finger measuring volume changes in the fingertip (115). These methods are described in depth by Dahle et al. (115). Measurement of peripheral endothelial function was only performed in Norway and only in the HITTS 1-year follow-up study. All the endothelial assessments were

done by a dedicated nephrologist from the Oslo University Hospital blinded to the intervention.

3.13 Bioelectrical impedance analysis

Body composition was measured with segmental bioelectrical impedance analysis (BIA). With BIA, low electrical impulses are sent through the body and can differentiate between organ tissues with different resistances (116, 117). In Norway and Sweden, a Tanita InnerscanV model BC-545N (Tanita, Arlington, Heights, IL, USA) was used, while the center in Denmark used the Tanita model MC-780 MA. Both models have electrodes on the handles for the hands and under the feet and can measure the body composition in limbs as well as in the upper trunk. Some BIA models are validated against dual X-ray absorptiometry (DXA) and except of fat tissue mass, which BIA seem to underestimate, the two methods are comparable (116). Participants were measured after breakfast but before the exercise tests.

3.14 Echocardiography

Echocardiography was performed by blinded technicians and evaluated by experienced cardiologists in the clinic, as a routine assessment both at baseline and at the annual follow-ups at all three transplant centers.

3.15 Right heart catheterization

At Oslo University Hospital, Rikshospitalet, right heart catheterization is performed as a clinically routine by cardiologists at the Department of Cardiology before 12 weeks after HTx, 6 months after HTx and at the annual 1-year follow-up. The right heart catheterization method is described by Gude et al. (118). Data from this measurement was obtained from the

participants in Norway and in the 1-year follow-up study only. After the annual 1-year follow-up, right heart catheterization was performed on clinical recommendation only. Right heart catheterization was therefore not measured in the HITTS 3-year follow-up cohort.

3.16 Arteriovenous oxygen difference (a-vO₂ diff)

The a-vO₂ diff was calculated according to the Fick equation (58) using the resting VO₂ values from the CPET and the cardiac output from right heart catheterization. For the reasons described in the previous section, the a-vO₂ diff was only measured in the Norwegian cohort and at the 1-year follow-up.

3.17 Biochemistry

Blood samples at both HITTS 1-year (Norway, Sweden, and Denmark) and 3-year follow-ups (Norway) were taken at a fasting state in the morning before other clinical assessments. A research nurse was responsible for all the blood sampling. The method is described in depth in Paper 1 of this thesis.

3.18 Ambulatory blood pressure

Twenty-four-hour blood pressure was monitored ambulatory (Oscar 2, SunTech Medical, Inc.). For standardization, the blood pressure was also measured during the in-hospital study visits (from day 1 to day 2 at baseline, at 1-year follow-up and at 3-year follow-up).

3.19 Reporting adverse events and serious adverse events

HITTS 1-year follow-up

Between the start of the first intervention period and the 1-year follow-up, the physical therapists were told to report adverse events on the exercise logs or by phone calls with the in-hospital physical therapist. In addition, information about clinical status and events were reported by the patients themselves at 6- and 12-month follow-up. The participants' medical records were screened as well.

HITTS 3-year follow-up

Information about clinical events (rejections, infections, cancer, cardiovascular, lung, gastrointestinal, anemia, musculoskeletal, pain and other symptoms affecting daily life or causing hospitalization) during the three years of follow-up were reported from the medical records (from the three annual follow-ups) in the participants included in the HITTS 3-year follow-up. The information was used to investigate whether there were any differences between the two groups in adverse events in the long-term.

3.20 Self-reported questionnaires

Health-related quality of life

HRQoL was measured at baseline, at 1-year follow-up and at 3-year follow-up with SF-36v2 (119), which is validated and the most frequently used HRQoL questionnaire among studies of HTx recipients (84). SF-36v2 is a generic questionnaire that measures HRQoL on eight subscales: Physical Functioning, Role-Physical, Bodily Pain, General Health Vitality, Social

Functioning, Role-Emotional and Mental Health. Physical Functioning indicates a respondent's ability to perform different physical activities in daily life related to physical health. Role-Physical is a respondent's ability to work or to do other role-related activities due to their physical health. Bodily Pain reflects a respondent's limitations due to pain. General Health is a respondent's perception of her or his own health. Vitality is a respondent's energy level in daily life. Social Functioning is a respondent's ability to be social due to their health. Role-Emotional is a respondent's ability to work or to do other role related activities due to emotional health. Mental Health indicates whether a respondent has symptoms of depression. Higher scores indicate better function and better health (119). These eight subscales are aggregated into two sum scores: A Physical Component Summary score and a Mental Component Summary score. All eight subscales contribute to the two sum scores, but the physical subscales contribute more to the Physical Component Summary score than the psychosocial related subscales, and vice versa. On advice of SF-36v2 manual, we used norm-based scores with a mean \pm SD of 50 ± 10 (119).

Symptoms of anxiety and depression

Symptoms of anxiety and depression were measured at baseline, at 1-year follow-up and at 3-year follow-up with the Hospital Anxiety and Depression Scale (HADS) (120, 121). HADS is validated and has been found to be an adequate measurement for assessing symptoms of anxiety and depression in patients suffering from somatic and mental illness as well as in the general population (122). HADS consists of 14 items scored 0–3, where seven items are related to symptoms of anxiety and seven to symptoms of depression (120, 121). The scoring manual (123) suggests that a score from 0–7 is considered to represent no symptoms of depression or anxiety.

Visual analogue scale

After the 9-month intervention period and at the 3-year follow-up, participants in both groups reported the subjective effects of the intervention on their general health and well-being on a 100 millimeter horizontal visual analogue scale (VAS) (124), ranging from “not at all” to “to a very great extent”.

Socio-demographic variables

The socio-demographic variables age, gender, social status, number of children, smoking habits, employment status and the participants willingness to go back to work were reported on a questionnaire attached to the other questionnaires.

Self-reported physical activity

At the 3-year follow-up, participants were asked to record questions about physical activity with questions adapted from the HUNT3 study (*Helseundersøkelsen i Nord-Trøndelag*) (125). The questionnaire consisted of questions about frequency, durability and intensity of physical activity performed the last three months, and also a question about the amount of time during a day spent sitting. The Norwegian term “mosjon” used in the physical questionnaire can be translated both into exercise and physical activity, and the definition of the term has previously been discussed (126, p. 21 , 127, 128). “Mosjon” as used in the questionnaire includes physical activities like “go for walks, swimming, skiing, doing work outs or sports” (126, p. 21 , 127). It is however not specified if this activity is structured, planned, or repetitive, and “mosjon” refers more to physical activity than exercise as it defined in this thesis. We coded the answers about physical activity as described by Kurze et al. (129). The question about frequency was coded as 0 = Never, 0.5 = less than once per week, 1 = once per week, 2.5 = 2–3 times per week, 5= Almost every day. The codes to the intensity question

were 1= Easy, no sweat or breathlessness, 2 = pushing hard, losing breath and becoming sweaty, 3 = pushing to nearly exhaustion. The codes to the question about duration were 0.10 = 15 minutes, 0.38 = 15–29 minutes, 0.75 = 30 minutes to 1 hour, 1 = 1 hour. A physical activity index has been found to be valid and this was calculated by the product of frequency, intensity, and duration (129). The participants were also asked to report whether they were in daily physical activity in 30 minutes or more at work and/or in leisure time.

3.21 Activity monitor

In the HITTS 3-year follow-up study, daily physical activities were monitored by the SenseWear Armband Mini (BodyMedia Inc., Pittsburgh, PA, USA) (130). The SenseWear Armband Mini is a three-axis accelerometer which also estimates energy expenditure by heat-related variables (heat changes, skin temperature and galvanic skin response) (131). The SenseWear Armband has been validated against indirect calorimetry in cardiac patients (132), against indirect calorimetry and other activity monitors in healthy adults (133), and across age-groups (134). It has been used in cardiac rehabilitation (135) and in the HTx population in particular (25). The participants were instructed in how to attach the activity monitor to the triceps brachii musculature before they left the hospital visit for the 3-year follow-up. The participants were asked to use the armband for seven days at home during the week after the study visit and mail it back to the study center as soon thereafter as possible. Participants with ≥ 3 monitored weekdays were included in the analyses of data. The data was analyzed with SenseWear Professional Software 8.1 (130). The physical activity intensity levels were reported as metabolic equivalents (METs) (136, 137) and categorized as sedentary (< 1.5 METs), light (1.5–2.9 METs), moderate (3–5.9 METs), vigorous (6.0–9.0 METs) and very vigorous (> 9.0 METs). The duration of physical activity at the different intensity levels were reported in minutes.

3.22 Power calculation

The power calculation for the study was published in the design paper (106). Since no other studies with these exercise interventions in the early phase after HTx had been published, the power calculation was based on previous studies in maintenance HTx recipients (22, 23), and a mean change in $VO_{2\text{peak}}$ of 5–7 mL/kg/min was expected. The mean difference between the groups after intervention was assumed to be 3 mL/kg/min with a SD of 5 mL/kg/min. For an α of 5% and a power of 80%, at least 44 patients were needed in each group. Initially we described that 120 participants would be included with the purpose of compensating for drop-outs and for more robust analyses on secondary endpoints (106). The inclusion lasted longer than expected due to fewer transplantations in the collaboration centers during the inclusion period, and in the end we managed to include only 81 patients (Paper 1 and Paper 2).

3.23 Statistical analyses

Statistical analyses were performed with IBM SPSS version 23 (Paper 1) and version 25 (Papers 1–4) (IBM corporation, Armonk, NY.). Continuous variables are presented as mean \pm SD, median (interquartile range) or (first quartile, third quartile) (Paper 1). Categorical variables are presented as number and/or percentages.

In Paper 1, the data was divided into two groups based on the $VO_{2\text{peak}}$ median value, and comparisons between groups were assessed by independent t-tests or Mann-Whitney U-tests for continuous variables. Pearson's chi-square or Fisher's exact test were used for categorical data.

Mean differences between the HIT and MICT groups were assessed by independent sample t-tests or Mann-Whitney U-test as appropriate. In Paper 2, baseline adjusted analysis of

covariance (ANCOVA) was used for comparison and verification of the t-test analyses. For categorical data, differences between groups were analyzed with Pearson's chi-square test or Fisher's exact test. Mean changes within groups were analyzed with paired sampled t-test or Wilcoxon signed rank test (Papers 2–4).

Bivariate relationships were assessed by Pearson's r or Spearman's rho correlation analyses (Papers 1–4).

In Papers 1 and 2, univariate associations between the dependent variable VO_{2peak} and independent variables were analyzed with linear regression. Significant variables ($p < 0.05$) and other potential variables were assessed by multiple regression analysis with the forced entry (enter) method.

In Papers 1–4, the data were checked for normality, linearity and homogeneity of variance. When running the regression analyses (Papers 1 and 2), data were checked for multicollinearity, interactions and homoscedasticity. The level of significance was set to $p < 0.05$ (two-sided).

4 Summary of results

4.1 Paper 1

Clinical features and determinants of VO_{2peak} in *de novo* heart transplant recipients

Eighty-one HTx recipients performed a CPET, reported HRQoL and underwent a clinical examination mean 11 ± 1.8 weeks after HTx. Mean age was 49 ± 13 years, 73% were men. The mean VO_{2peak} was 20.4 mL/kg/min which was 56% of age-predicted values (138) and median VO_{2peak} in the cohort was 19.4 mL/kg/min. The population was divided into two groups according to the median VO_{2peak} value, a high-capacity group and a low-capacity group. There were significant differences between the two groups clinically (body composition, medication, biomarkers, heart function, lung function) and in cardiopulmonary responses to exercise, muscle strength, and HRQoL. A positive and strong correlation was found between VO_{2peak} L/min and O_2 pulse (Pearson's $r = 0.804$) and between VO_{2peak} and muscular exercise capacity (Pearson's $r = 0.637$). A moderate and positive correlation was found between VO_{2peak} and heart rate reserve (HRR) (Pearson's $r = 0.473$). In the multiple regression analysis, O_2 pulse, HRR, muscular exercise capacity, BMI, sex and age accounted for 84% of the variance. The significant predictors for early VO_{2peak} in the multiple regression model were O_2 pulse, HRR, and muscular exercise capacity.

4.2 Paper 2

Effect of High-Intensity Interval Training in De Novo Heart Transplant Recipients in Scandinavia: One-Year Follow-Up of the HITTS Randomized, Controlled Study

The HITTS study compared HIT versus MICT using a prospective multicenter randomized controlled study with participants from three transplant centers in Scandinavia. Participants

were randomized to either HIT or MICT, and both groups were followed by local physical therapists in their local communities. The exercise interventions lasted for nine months and both groups exercised 2–3 times per week. All exercise sessions were logged and monitored with a heart rate monitor.

Seventy-eight of the 81 initial participants completed the study. After nine months of exercise intervention, the HIT group had a higher mean change in VO_{2peak} than the MICT group (Figure 11). This difference was 1.8 mL/kg/min, which is regarded clinically significant.

Additionally, the HIT group had a significantly higher AT, peak expiratory flow, and muscular exercise capacities of the extensors. Within-group analyses showed that the MICT group also improved the VO_{2peak} during the intervention period. No adverse events related to exercise in either of the group were reported during the intervention period. Some participants were not able to perform all of the planned exercise sessions for various reasons (supplementary Table 7 in Paper 2).

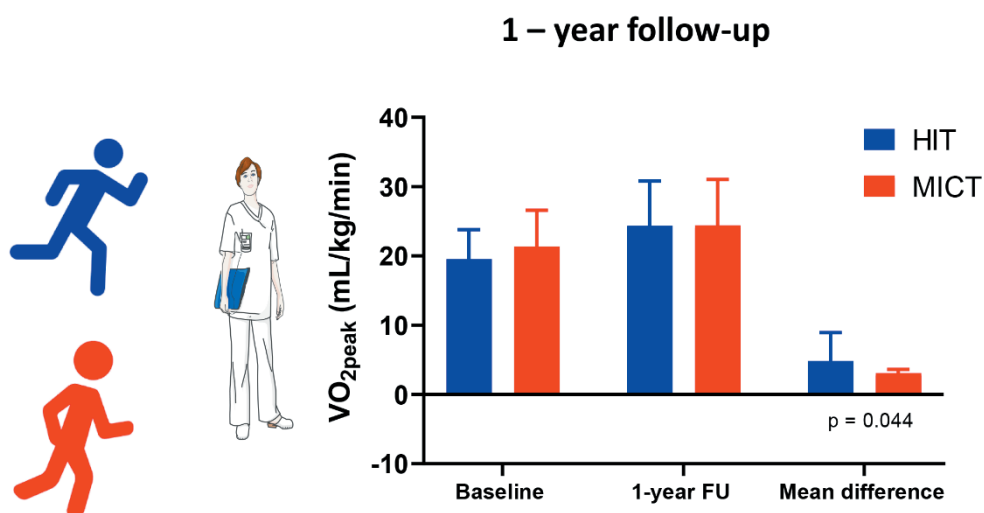
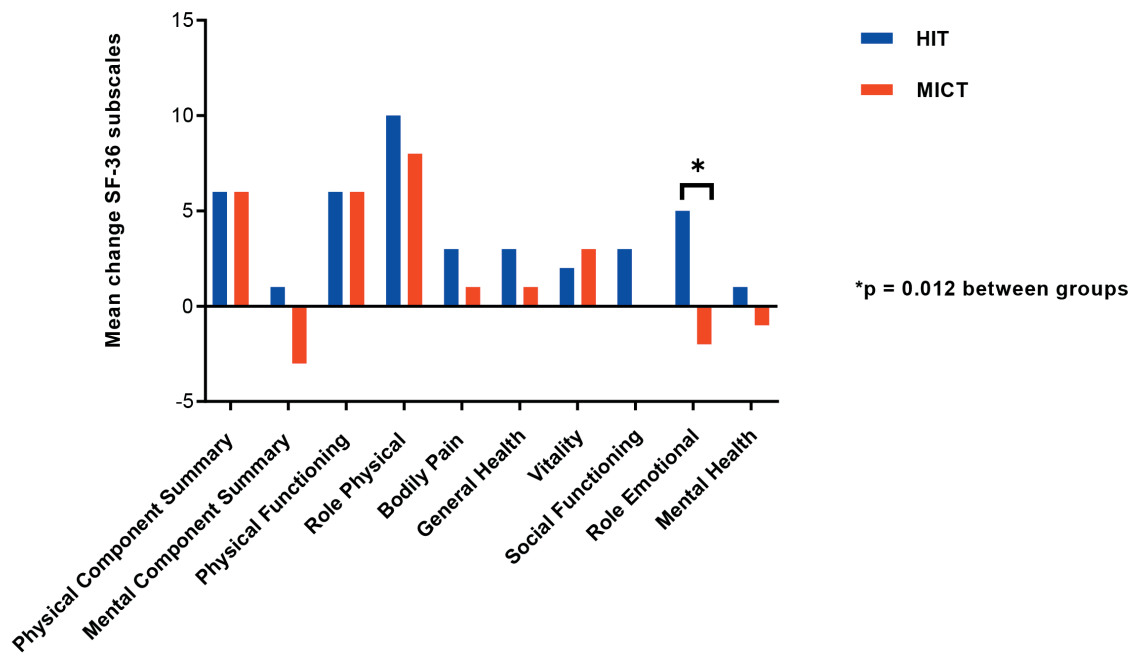


Figure 11 Graphical visualization of the main results from the 1-year follow-up study.

4.3 Paper 3

High-intensity interval training and health-related quality of life in de novo heart transplant recipients – results from a randomized controlled trial

This paper is a sub-study of the HITTS 1-year follow-up. Here, we investigated the effect of HIT versus MICT on HRQoL in *de novo* HTx recipients. Both the HIT group and the MICT group had a significant increase in the subscales Physical Functioning, Role Physical, and Physical Component Summary scores on the SF-36 questionnaire during the 9-month intervention period. In both groups, the Mental Component Summary scores (SF-36) were high with mean scores above 50 at baseline and remained high at 1-year follow-up. Only one difference between the two groups was seen in HRQoL sum-scores and subscales, namely the Role-Emotional subscale, with the HIT group scoring significantly higher (Figure 12). Self-reported physical function had a positive, moderate correlation with both VO_{2peak} and muscle strength in both groups at both baseline and at 1-year follow-up. Symptoms of depression and anxiety were low in both groups and stable through the intervention period.



SF-36 summary scores and subscales

Figure 12 Mean change in SF-36 summary scores and subscale scores between the baseline and the 1-year follow up. Comparison between groups.

4.4 Paper 4

Long-term effects of high intensity training vs moderate training in heart transplant recipients: A 3-year follow-up study of the randomized-controlled HITTS study

The HITTS study with 3-year follow-up is an extended study of the HITTS 1-year follow-up study with participants from Norway only. The aim of the HITTS 3-year follow-up was to study the long-term effects of early initiation of HIT versus MICT.

Of the 78 participants in the HITTS 1-year follow-up trial, 62 completed the 3-year follow-up.

The mean age of participants \pm SD was 52 ± 13 and 76% were men. The between-groups

mean change in $VO_{2\text{peak}}$ mL/kg/min between baseline scores and the 3-year follow-up (Figure 13) was 1.7 mL/kg/min, but this difference was not statistically significant. The difference between groups in mean change in $VO_{2\text{peak}}$ L/min was nearly significant, with the HIT group showing greater improvement (0.2 L/min, $p = 0.053$). The between-groups mean change in the muscular exercise capacities of the extensors and AT was significant and sustained from one year after HTx, with a higher mean change in the HIT group than the MICT group. Additionally, a difference between groups in mean change in the muscular exercise capacities of the flexors between baseline and 3-year follow-up was significant, with the HIT group showing greater improvement. No other significant mean changes between baseline and 3-year, or between 1-year and 3-year follow-ups, were observed. The HIT group declined less in $VO_{2\text{peak}}$ after the 1-year follow-up than the MICT group (Figure 13). Additionally, the decline in exercise capacity observed in the HIT group was smaller than the expected age-related changes in $VO_{2\text{peak}}$.

HRQoL scores (both physical and mental summary scores) were high at 3-year follow up and were in line with the age-and sex adjusted general population.

According to self-reported data on physical activity at 3-year follow-up, a majority of the participants were physically active for 30 minutes daily at work or in the leisure time, 85% in the HIT group versus 91% in the MICT group. In the HIT group, 79% of the participants versus 82% of the participants in the MICT group, performed physical activities (walks, swimming, skiing, work outs or sports) ≥ 2 times per week or more. In both groups, most participants were performing physical activities at moderate intensity (HIT group, 69% versus MICT group, 66%). Only a few participants in both groups reported to do physical activities with high intensity (“pushing to near exhaustion”).

The activity monitors showed that participants in both groups had more than 30 minutes (mean) daily activity with moderate intensity, with 81 ± 53 minutes in the HIT group versus

78 ± 46 minutes in the MICT group. There were no differences between the two groups in self-reported physical activity levels or physical activity as measured by activity monitors.

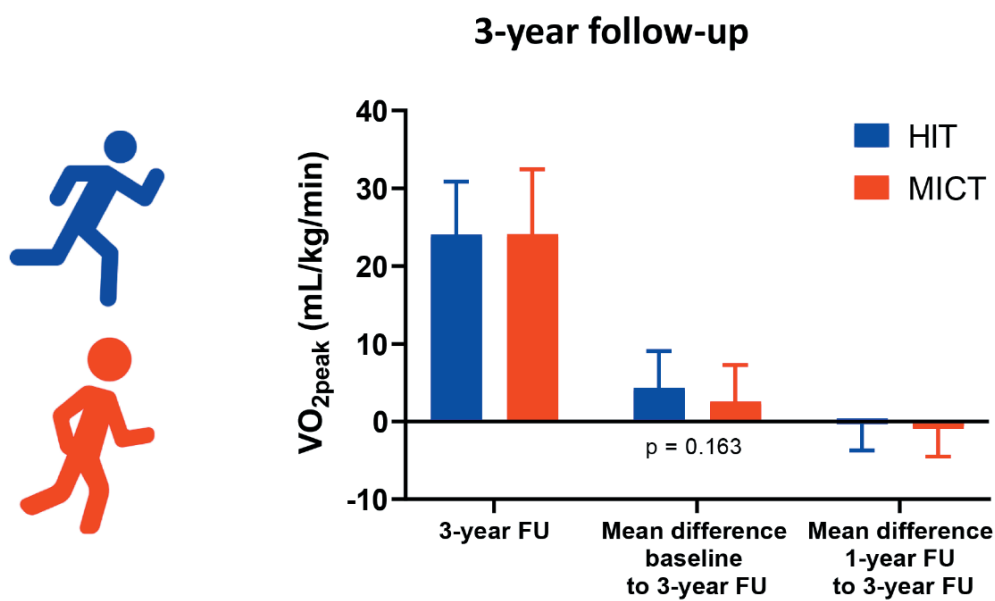


Figure 13 Graphical visualization of the main results from the 3-year follow-up study.

4.5 Supplementary results

4.5.1 Adverse/serious adverse events

There were no significant differences between HIT and MICT according to number or type of rejections (Table 4) or in number of adverse events during the three years of follow-up (Table 5).

Table 4 Number of rejections during the three years of follow-up (a single participant may have more than one rejection).

Type and grade of rejections	HIT n=28 (MICT n=34)			
	Initial rejections	From inclusion to 1st year	2nd year	3rd year
Rejection grade 1 R	13 (13)	4 (7)	2 (2)	1 (1)
Rejection grade 2 R	2 (2)	0 (2)		1 (0)
AMR	0 (0)	0 (0)	4 (0)	2 (3)
Total number of rejections	15 (15)	4 (9)	6 (2)	4 (4)

AMR, antibody-mediated rejection.

Table 5 Number of adverse events during the three years of follow-up (a single participant may have more than one event).

Number of adverse events	HIT n=28 (MICT n=34)		
	1st year	2nd year	3rd year
Musculoskeletal	3 (4)	1 (3)	1 (3)
CMV infections	4 (3)	0 (1)	0 (0)
Other infections (non-hospitalized)	2 (5)	0 (4)	2 (3)
Other infections (hospitalized)	3 (4)	4 (3)	0 (1)
Pain (head/foot)	2 (0)	1 (0)	1 (2)
Gastrointestinal problems	1 (3)	2 (0)	1 (1)
Hernia	2 (2)	1 (0)	1 (1)
Sudden drop in heart rate	0 (1)	0 (0)	0 (0)
Heart palpations	1 (1)	2 (0)	3 (0)
Tachycardia	1 (0)	0 (1)	1 (0)
Deep vein thrombosis	1 (0)	0 (0)	1 (0)
Claudicatio intermittens	1 (0)	0 (0)	0 (0)
Dyspnoea	1 (0)	2 (1)	1 (1)
Operated ASD	0 (1)	0 (0)	0 (0)
Hyperthyroidism	1 (0)	0 (0)	0 (0)
Diabetes II	1 (0)	0 (0)	0 (0)
Removed sternal steel wire	1 (1)	0 (0)	0 (0)
Pulmonary embolism	0 (0)	1 (0)	2 (0)
Densification on pulmonary x-ray	0 (0)	1 (0)	1 (0)

Infrarenal aneurysm (operation indicated)	0 (0)	0 (1)	0 (0)
Orthostatic syncope	0 (0)	3 (0)	0 (0)
Depression/anxiety	0 (0)	0 (1)	0 (0)
Lymphocele sclerosis	0 (0)	0 (1)	0 (0)
Pulmonary hypertension	0 (0)	1 (0)	0 (0)
Anemia (hospitalized)	0 (0)	0 (1)	0 (0)
Dermal transplant due to wound on the foot	0 (0)	0 (1)	0 (0)
Squamous cell carcinoma	0 (0)	1 (0)	1 (0)
Increased NT-ProBNP (suspected acute rejection, steroid treatment, biopsy negative)	0 (0)	1 (0)	1 (0)
Cramps (finger and toes)	0 (0)	1 (0)	0 (0)
Thrombectomy (lower extremity)	0 (0)	0 (0)	0 (1)
Percutaneous transluminal angioplasty	0 (0)	0 (0)	0 (1)
Bradycardia	0 (0)	0 (0)	1 (0)
Pulmonary cancer (lobectomy)	0 (0)	0 (0)	1 (0)
Small cerebral infarction	0 (0)	0 (0)	1 (0)
Mitral insufficiency	0 (0)	0 (0)	1 (0)
Tonsil cancer	0 (0)	0 (0)	0 (1)
Pulmonary abscess	0 (0)	0 (0)	0 (1)
Removed bulge behind eye	0 (0)	0 (0)	0 (1)
Total number of events	25 (25)	22 (18)	21 (17)

ASD, atrial septal defect; CMV, cytomegalovirus; NT-ProBNP, N-Terminal pro-B-type natriuretic peptide

5 Discussion

The last 10–15 years of exercise research in the field of HTx can be described as a paradigm shift in exercise-based cardiac rehabilitation for this population. The exercise restrictions based on the denervated heart have been refuted by randomized controlled studies showing the feasibility and efficacy of HIT in maintenance HTx recipients (22, 23, 26). As mentioned in the introduction of this thesis, there is now consensus that the exercise guidelines after HTx should be updated (11). The work described in this thesis comparing HIT to MICT in the *de novo* HTx recipients with both short and long-term follow-up contribute new knowledge to this field.

The main finding in this study was that HIT seems to be a safe and effective method of exercise for the *de novo* HTx recipient. During a 9-month follow-up period of supervised HIT and MICT exercise programs, HIT resulted in a significant average improvement in VO_{2peak} . The mean difference between groups seen in our study of 1.8 mL/kg/min (approximately $\frac{1}{2}$ MET) seems to be a clinically important difference, and it is larger than observed differences in studies of heart failure patients that compare exercise to no exercise (139), beta-blockers versus placebo (140), or in patients treated with cardiac resynchronization therapy versus usual care (141).

This is the first study showing the feasibility and effectiveness of HIT in the early phase after HTx in a decentralized setting with long-term follow-up. We have demonstrated that HIT can be supervised by local physical therapists outside the transplant centers and that HTx recipients are able to perform HIT sessions 2–3 times per week with a denervated heart.

The physical function domains of HRQoL increased significantly between the baseline and the 1-year follow-up in both HIT and MICT participants, with no mean difference between groups. The HRQoL summary scores were high in both groups one year after HTx, with mean

scores nearby or above 50. The 3-year follow-up study showed no statistically significant mean differences between the groups in VO_{2peak} between baseline and the 3-year follow-up. However, the HIT group declined less in VO_{2peak} between the 1-year follow-up and the 3-year follow-up, and the decline was smaller than the expected age-related decline seen in the general population. We also found a sustained significant mean improvement in AT and muscular exercise capacities of the extensors in the HIT group. The HRQoL summary scores remained high at 3-year follow-up, with no differences between the two groups.

In the HITTS cohort, a high proportion in both groups, had more than 30 minutes daily physical activity three years after HTx, however, only a few of the participants continued with HIT.

5.1 Effect of HIT versus MICT on VO_{2peak}

The superior effect of HIT versus MICT on VO_{2peak} in the early phase after HTx found in our study (Paper 2) is in line with the findings of Dall et al. (26) in maintenance HTx recipients. Although there was greater improvement of the HIT group in both studies, it must be noted that the within group difference was significant both in the HIT group and in the MICT group in both studies. HIT might not be the preferred method for every HTx patient, and so an important message is that MICT also has favorable effects on VO_{2peak} both in the early phase (< 1 year after HTx) and later on (> 1 year after HTx). In the earliest phase (< 6 months after HTx), MICT is probably good enough for the average HTx patient. Systematic HIT will probably be easier to perform six months after HTx and also more effective at that time. Studies comparing different exercise modalities versus control groups with no structured exercise programs at different time points after HTx clearly show that structured exercise programs increase the VO_{2peak} more than the alternatives (5, 20-23, 77, 142, 143), and these

results underscores the importance of a systematic exercise-based rehabilitation program for higher physical fitness after HTx.

The long-term effects of HIT on VO_{2peak} have not been investigated until recently. In the first study by Yardley et al. (25), in maintenance HTx recipients there was no statistically significant difference between HIT and the control group (no exercise intervention) in VO_{2peak} four years after the intervention period had ended. However, in contrast to the HIT group, the control group had a significant decline in VO_{2peak} between baseline scores and the 5-year follow-up. In the HITTS study (Paper 4), no significant difference between HIT and MICT in VO_{2peak} was seen between baseline and the 3-year follow-up, but the mean difference between the two groups was still 1.7 mL/kg/min (compared to 1.8 mL/kg/min at the 1-year follow-up). At the 3-year follow-up, the number of participants was reduced to 62 (from 78 at the 1-year follow-up), and perhaps the mean difference between groups would probably remained significant at the 3-year follow-up if the number of participants was higher.

In the HITTS 3-year follow-up study (Paper 4), there was only a small non-statistically significant decline in VO_{2peak} in both groups between the 1-year follow-up and the 3-year follow-up, and this decline was less in the HIT group than the MICT group. The results from both Yardley et al. (25) and the HITTS 3-year follow-up study (Paper 4) indicate that exercise-based cardiac rehabilitation has positive long-term effects on the decline in VO_{2peak} .

In addition, the decline in VO_{2peak} in the HITTS study (Paper 4) two years after the exercise intervention ended was comparable to the expected age-dependent decline in the general population (144). A similar pattern has been found in other long-term studies following HTx participants after exercise training programs (25, 64). Although the HTx recipients participating in exercise studies have not been able to maintain the same exercise intensity as they did during the interventions, the smaller age-related decline in VO_{2peak} might have a positive impact on survival (4, 5).

It should be noticed that the deterioration in VO_{2peak} seen in the HITTS study between the 1-year follow-up and the 3-year follow-up was smaller in HIT group (-0.3 mL/kg/min) than the MICT group (-0.9 mL/kg/min), which might indicate some sustainable effects of HIT versus MICT after the intervention has been ended. For comparison, in the study by Yardley et al. (25) in maintenance HTx recipients, the HIT group had a decline of -1.75 mL/kg/min versus a control-group decline of -2.78 mL/kg/min. These differences might indicate a favorable effect of early cardiac rehabilitation on the sustainability of VO_{2peak} in the long-term post HTx.

The importance of early cardiac rehabilitation on other endpoints not captured in this thesis should also be mentioned. Rosenbaum et al. (145) found an association between early cardiac rehabilitation and long-term survival in HTx recipients at the Mayo Clinic, USA. Bachmann et al. (146) have reported that those who participate in cardiac rehabilitation in the early phase after HTx have a lower risk for readmission during the first year post HTx than those who did not engage in such a program.

5.2 Effects of HIT versus MICT on skeletal muscular system

The HITTS study is the first study showing superior effects of HIT compared to MICT on the muscular exercise capacities of the extensors in both the short-term (Paper 2) and in the long-term (Paper 4) after HTx. The favorable effects of exercise on skeletal muscle morphology (51, 142, 147), the increase in lean body mass (19, 21, 51), and increase in muscular strength (21, 23, 50, 51, 76) have been shown previously after HTx. The effect of HIT on muscular strength is interesting. In the TEX study (23), the HIT group increased muscular exercise capacity significantly without any specific strength training intervention. In the HITTS study (Paper 2), the HIT group and the MICT group performed the same general strength training program. Nevertheless, we found a significant mean improvement in the change in muscular exercise capacities of the extensors in the HIT group.

The favorable effects of HIT versus MICT on muscular exercise capacities of the extensors was still noticeable at 3-year follow-up (Paper 4). These results might indicate a certain effect of HIT versus MICT on the skeletal muscular system. Possible mechanisms behind this “HIT effect” have been reported by Yardley et al. (5, 148), who found a higher increase of vascular endothelial growth factor (VEGF-1) and angiopoietin-2 (Ang-2) immediately after a HIT session than after a MICT session in maintenance HTx recipients. VEGF-1 is a pro-angiogenic factor that contributes to capillary growth in skeletal muscle (149), while Ang-2 facilitates new vessels sprouting from existing vessels (150). In the HITTS study, we did not investigate the acute effects of HIT and MICT on the biomarkers described by Yardley et al. (148), and so we cannot offer evidence of these potential mechanisms. However, the topic is interesting and should be studied in larger trials with HTx recipients.

5.3 Effect of HIT versus MICT on a-vO₂ diff

The a-vO₂ diff is of interest when studying the effects of exercise after HTx (45, 151). In the HITTS 1-year follow-up study (Paper 2), no difference between a-vO₂ diff in the HIT and MICT group was found. No other studies have looked at the effect of HIT versus MICT on a-vO₂ diff after HTx, but a small study with seven HTx participants found no effect of exercise training on a-vO₂ diff during submaximal exercise testing (151). In our study, the a-vO₂ diff was calculated from resting variables, which is a methodological limitation in our study (see Chapter 6, “Methodological considerations”). An exercise study of heart failure patients with preserved ejection fraction showed increased a-vO₂ diff after 12 weeks of aerobic interval training at an intensity of 80% of VO_{2peak} (152), and it is possible that a similar result might have occurred in the HITTS 1-year follow-up study (Paper 2), if a-vO₂ diff had been calculated from peak exercise.

5.4 Effect of HIT versus MICT on endothelial function

No differences between the HIT group and the MICT group were found in endothelial function measured by EndoPAT and FMD (Paper 2) which is in line with the results of Dall et al. (91) in maintenance HTx recipients. In contrast, Herman et al. (22) found a significant effect on endothelial function (increased brachial artery flow mediated dilatation) in the HIT group compared to usual care (no specific exercise). In Paper 2 and Dall et al. (91), endothelial function was a secondary endpoint and a type II error might have occurred.

5.5 Predictors of VO_{2peak} in the *de novo* heart transplant recipients

The aim at baseline (Paper 1) was to investigate predictors of early VO_{2peak} in *de novo* HTx recipients, and this the primary aim became a secondary aim the HITTS 1-year follow-up study (Paper 2). Previously, we had shown that peripheral factors (muscular exercise capacity and body fat) were stronger predictors for VO_{2peak} than central factors (chronotropic responses) > 1 year after HTx (111). In contrast, in this *de novo* HTx HITTS-cohort, we found that central factors (O_2 pulse and HRR) were stronger predictors of early VO_{2peak} than peripheral factors (Paper 1). At the 1-year follow-up, we also found that central factors (peak heart rate and O_2 pulse) contributed more to the mean change in VO_{2peak} than muscular capacity to the mean change in VO_{2peak} (Paper 2). This relationship seems reasonable due to the denervated heart and severe chronotropic incompetence, especially the first months after HTx (41, 153). O_2 pulse measured during CPET is considered by some to be a surrogate for stroke volume (28, 29, 154, 155). We therefore defined O_2 pulse as a central factor in our analyses. However, it is important to be aware of the component of a peripheral factor (oxygen extraction) in O_2 pulse (156). In the absence of a non-invasive method for directly measuring stroke volume during maximal exercise, we found O_2 pulse to be the most accurate method for estimating stroke volume.

Although we found that the central factors were stronger predictors for VO_{2peak} in the early phase after HTx, peripheral factors are nevertheless highly important. In the long term after HTx, both body composition and muscular exercise capacity are shown to be strong predictors of change in VO_{2peak} after an exercise training intervention (45, 111).

5.6 Effect of HIT versus MICT on heart function

The beneficial effects of HIT compared to MICT on cardiac function in patients with cardiovascular diseases has previously been reported (157) and has been explained by exercise intensities of > 85% of maximal effort being able to increase the cardiac pump function (157, 158). However, trials in cardiovascular diseases have shown conflicting results of the effect of HIT on left ventricular function (38, 159). A study by Wisløff et al. (38) showed that left ventricular function improved in the HIT group and with a significant difference between HIT and MICT (38). In the SMART-EX study (Study of Myocardial Recovery after Exercise Training in Heart Failure), no differences were found between HIT and MICT in left ventricular end-diastolic diameter and left ventricular ejection fraction (159). The effect of exercise on left ventricular function has been less studied in the HTx population. In the HITTS study, both at 1-year follow-up and 3-year follow-up, there was no mean difference between HIT and MICT on left ventricle function assessed by echocardiography at rest (Papers 2 and 4). These results are in line with studies in maintenance HTx recipients that compare HIT to non-exercise controls both in the short-term (21, 160, 161) and long-term (25).

In the HITTS 1-year follow-up study (Paper 2), heart function was also measured by right heart catheterization at rest. No differences were found between HIT and MICT in either of the data obtained during the procedure.

5.7 Effect of HIT versus MICT on body composition

In the HITTS study, both groups significantly gained weight and increased their amount of body fat during the intervention period (Paper 2), more so in the HIT group than the MICT group. In contrast, in the TEX study, body composition remained stable in both the HIT group and the non-exercise group in the 1-yr follow-up (23). The weight gain observed in the HITTS study 1-yr follow-up is commonly seen in clinical practice the first year after HTx (162, 163) and has been shown to stabilize thereafter (164). Some of the difference between the HITTS study (Paper 2) and the TEX study might be because of changes in body composition.

5.8 Effect of HIT versus MICT on health-related quality of life and mental health

In the HITTS 1-year follow up study, we found no difference in HRQoL between HIT and MICT as measured by SF-36v2 on seven of the eight subscales (Paper 3), and these results are in line with Dall et al. (91) on HIT versus MICT in maintenance HTx recipients. Another similar finding of the two studies was that the Physical Functioning subscale and the Physical Component Summary score increased within both groups during the intervention period. Exercise in general seem to have an impact on the physical domains in HRQoL after HTx, but the intensity of the exercise does not seem to be as important. However, in the HITTS 1-year follow up study (Paper 3), we found a significant mean difference between groups in change of the Role Emotional subscale, and the improvement was greater in the HIT group. This result might be a consequence of increased self-efficacy after HIT. Self-efficacy is described as a measure of self-confidence in relation to performing certain physical tasks and has been shown to increase with exercise training in patients with cardiac disorders (165, 166). In a study of high-intensity strength training versus flexibility training added to a cardiac

rehabilitation program, self-efficacy scores and the emotional role scale were significantly higher in the high-intensity strength group than the flexibility training group (167). We did not measure self-efficacy in our study, so we cannot draw any conclusions, but from a theoretical point of view it is an interesting discussion.

Mental health as measured by SF-36 and the HADS were stable throughout the intervention period in both groups. Studies of maintenance HTx recipients investigating HIT versus a control group with no specific exercise showed a significant and positive effect of HIT on anxiety (25, 92), and an increased score on the mental health domain in SF-36 (92). The Role Emotional subscale in SF-36 measures problems at work or other activities in daily life due to mental health problems (119, 168, 169). The findings from all the three studies might indicate that HIT after HTx has some benefits for mental health.

5.9 Physical activity in the long term after HTx

Staying motivated for daily physical activity and keeping good exercise routines are challenging for solid organ recipients (170). In the HITTS 3-year follow-up study (Paper 4), participants in both groups on average had high levels of physical activity compared to that which is recommended in the healthy population (171). However, most of the participants did not do high intensity physical activity on a regularly basis after the end of the intervention period (Paper 4). Yardley et al. (25) found similar results in the 5-year follow-up of HIT versus control (no specific exercise) in maintenance HTx recipients. HIT and especially the 4 x 4 model is quite ambitious, and seems to be tough to perform without supervision, going by observations from both the HITTS 3-year follow-up study (Paper 4) and the TEX 5-year follow-up study (25) (which also used a 4 x 4 model). Although the participants did not sustain HIT, the participants in both Paper 4 and Yardley et al. (25) were highly physically active in daily life. The participants in both of these studies were on average more physical

active than reported in other non-exercise studies in the HTx population (66, 70, 72, 170, 172, 173). The recently published guidelines for physical activity and sedentary behavior from the World Health Organization highlights that any physical activity is better than none, and that minimizing sedentary behavior will have positive effects on health (171). Thus, we should encourage HTx recipients to stay physically active and focus on the benefits of doing daily physical activities. At the same time, they should be informed of the extra benefits of doing a little bit more, or at least the recommended ≥ 150 minutes of moderate-intensity exercise or 75 minutes of vigorous-intensity exercise per week, or a combination of these physical activity intensities (171).

5.10 Decentralized rehabilitation model

The need for and use of individualized cardiac rehabilitation models (as opposed to traditional in-hospital cardiac rehabilitation) is well-known (174-176). In the HITTS study, we found that HIT could be performed near the HTx recipients' homes under supervision of physical therapists, thus proving the feasibility of decentralized rehabilitation in the early phase after HTx. In Norway, this rehabilitation model is of special interest, both because of the large geographical distribution of the population and the semi-decentralized health care system (177). In 2012, coordination reform was established in Norway in order to improve collaboration between specialist and the primary health care services (177). The same year, we prepared the HITTS protocol and the rehabilitation model used was in accordance with the coordination reform, which could strengthen the clinical implications of the HITTS study (Paper 2). The need for rehabilitation programs to be accessible to organ transplant recipients in rural settings outside transplant centers has also been addressed in Canada (178). There is a gap in the research about creating and implementing rehabilitation programs outside transplant centers (10). The HITTS study is an example of how such non-centralized

rehabilitation can be done. Home-based or telehealth exercise programs as well as e-health applications with exercise prescriptions should be of interest for future research (10).

5.11 Safety, tolerability and adverse events

The first year after HTx is considered the critical year, and survival rates from the International Society for Heart and Lung Transplantation (ISHLT) are divided into overall survival and 1-year survival (179). Although no adverse events related to exercise were observed during the 9-month intervention period, various adverse events were reported during the intervention period. Different types of infections were especially common in both groups in the first year after HTx. Infections after HTx can have fatal consequences, and complications after infections are the main causes of death the first year (179). Participants with an ongoing infection were advised to take a break from HIT until they were medically cleared by the general practitioner and/or the transplant consultant. The same recommendations were given to those with a grade 1 rejection (mild rejection) or grade 2 rejection (moderate). Both infections and rejections are common in the early period after HTx (83) and it is important to be aware of any medical symptoms indicative of these problems. If diagnosed, patients are strongly recommended to exercise at only moderate intensity or to do only light physical activity until medical clearance. In cases of grade 3 rejection (severe rejection), patients should only do easy range-of-motion exercises (180). More and larger studies are needed before definite conclusions about the safety of exercise can be reached.

In general, long-term studies on the safety of HIT versus MICT in populations with cardiovascular diseases are scarce (181), and there are no studies published in the HTx population. In the HITTS 3-year follow-up study, adverse and severe adverse events were obtained from the medical records at the yearly annual follow-ups at Oslo University Hospital, Rikshospitalet. There was no difference between the two groups during the study

period in terms of adverse or severe adverse events. However, since there was no exercise intervention between the 1-year and the 3-year follow-up in the HITTS study, we cannot relate the events (> 1-year) to either of the two exercise modalities. The information is valuable in simply for increasing knowledge about this *de novo* HTx patients cohort who were included in an exercise study in the early phase after HTx.

5.12 Assessments of exercise capacity and physical activity

The importance of assessing exercise capacity after HTx has already been addressed in relation to the association between VO_{2peak} and survival (4). Impaired exercise tolerance has been associated with CAV, and performing a CPET at the first annual screening after HTx has been suggested as a method to identify patients at risk for developing advanced CAV (182). From a rehabilitation perspective, exercise testing is a useful tool to prescribe in order to evaluate the progress of a patient's exercise-based cardiac rehabilitation program after HTx (10, 183). CPET is the preferred method for measuring exercise capacity, but the method is resource-demanding and is only used the first year after HTx as a clinical routine in Norway (Paper 1). However, in recent years, measuring cardiorespiratory fitness has been suggested as a part of the general health screening (32, 184) and as a routine assessment both before and after solid organ transplantation (10). Measurements other than CPET might be an alternative if CPET is impractical or too costly in the clinical setting. The six-minute walk test is an easy test to perform and has shown a moderate correlation with VO_{2peak} among HTx recipients > 1 year after transplantation (185, 186). Another aspect of exercise testing after HTx, especially in the early phase after HTx, is that it increases confidence in exercising with the new heart, as discussed in Paper 1. Later on, regular exercise testing performed by experienced health personnel, together with guidance on exercise prescriptions, might motivate patients to be

more physically active, a process that has been described as facilitating increased physical activity after solid organ transplantation (72, 170)

6 Methodological considerations

Research is a systematic collection of data with prespecified methods. However, doing research is also a never-ending process of learning and failing. During the years of work with the HITTS study, we became aware of things we could have done differently and probably in a better way. Some of these aspects will be discussed in the next sections.

6.1 High-intensity interval exercise protocols

The duration and/or number of interval bouts in HIT is a constant topic of discussion. “How little is enough” to gain a certain effect? There is still no consensus of the optimal amount of HIT for achieving maximal health benefits, and the same HIT may have greatly different effects among individuals (36). In the last years, various studies have used different HIT exercise protocols in populations with cardiovascular diseases. In cardiac rehabilitation research, medium to long intervals (2–4 min at 85–95% of peak effort) are the most frequently used (187-189). In the HITTS study, we decided to use the 4 x 4 HIT protocol (4 high-intensity interval bouts at 85–95% of peak effort for 4 min, with 3 min recovery between bouts) (Figure 5) because this one is frequently used in Norway, and we were familiar with the protocol from previously research on HIT after HTx in our research group (23).

Although older patients with cardiovascular disease have been shown to tolerate and benefit from HIT in terms of exercise capacity, older patients might also have age-related complexities like frailty and multi-comorbidities which must be considered when prescribing HIT (190). The same considerations must be taken into account with the HTx population. In a small hypothesis-generating study comparing the effect of HIT on older and younger HTx recipients, the youngest group of patients seemed to benefit more from HIT in terms of VO_{2peak} and muscular strength than the older patients (191). It has suggested that older people

might respond better to a HIT protocol with shorter intervals of 1–2 min instead of 4 min (190) which might be an alternative for the older HTx recipients as well as those with comorbidities independent of age.

In the HITTS 3-year follow-up study, we found that only a few participants maintained HIT after the intervention with a 4 x 4 HIT protocol (Paper 4). The 4 x 4 HIT protocol might have been too demanding for the long-term for the HTx populations. One of the first studies comparing different HIT protocols (192) found that 1 x 4 min HIT and 4 x 4 HIT had similar effects on VO_{2peak} , blood pressure and work economy in a population of overweight but otherwise healthy men. If these results can be transferred to HTx recipients, the adherence and willingness to perform HIT in the long term will probably increase and be easier to implement in daily life. Ideas for further research are trials comparing the effect of different HIT protocols (i.e. comparing HIT with shorter and longer interval bouts) in HTx populations.

In the HITTS study, we did not use isocaloric exercise protocols (equal in energy exposure) (193), which might be a limitation of our study, because it has been suggested that isocaloric exercise protocols are important for knowing whether intensity is the leading factor for higher VO_{2peak} or not (194-196). On the other hand, isocaloricity and energy exposure of the training sessions is not a goal of its own in cardiac rehabilitation — more important is knowing what exercise modality is the most effective for improving VO_{2peak} (193), which was the main goal of the HITTS study. To control for this factor as much as possible, when we planned the study, we made sure that the MICT group did not have a lower exercise duration than the HIT group.

6.2 Reporting and monitoring exercise

An important part of this study was measuring the amount of exercise (frequency and intensity) during the 9-month intervention period in both groups. We only measured the supervised exercise sessions. In retrospect, it would have been useful to also measure the exercise the participant performed unsupervised. We do not know if there is a difference between the two groups in the *total* dose of exercise performed. The way the exercise sessions were reported is another aspect that we might have done differently if we were to repeat the study repeated today. An electronic reporting of the exercise sessions would have been more effective than the paper exercise logs we used in the HITTS study. The ideal way to both measure and report exercise would have been to have the participants wear an electronic device that communicated directly with the study center during exercise sessions (both supervised and unsupervised exercise). Many different electronic tracking solutions for exercise are available today and many of them have also been tested for clinical research use (197, 198). The preferred method would depend on cost and how user-friendly the device is, as well as how good the security was to address privacy and data protection concerns.

6.3 Days of wearing the activity monitor

In the HITTS 3-year follow-up study, we decided to include all participants that had ≥ 3 monitored days. Three to five days of monitoring has been suggested as sufficient for the adult population for reliable physical activity data from different accelerometers (199, 200). One study using the SenseWear Armband reported that, to obtain reliable habitual physical activity, at least three weekdays and both Sunday and Saturday would need to be monitored, because physical activity differs between weekdays and weekend days (201). In the HITTS study, we did not require one of the monitored days to be a weekend day. This might have

been a limitation to our study if the differences in physical activity on weekdays and weekend days were really so different.

6.4 Measures of exercise intensity in the *de novo* heart transplant recipient

In the HITTS study, we used both heart rate and RPE to measure the exercise intensity in both groups. The use of RPE (a subjective method) to ensure the desired exercise intensity is crucial in a *de novo* HTx patient with severely delayed heart rate response (180). The usefulness of a heart rate monitor in *de novo* HTx recipients should be emphasized in order to follow the changes that occur during the first year after HTx in heart rate response to exercise (41). Because heart rate response changed individually during the intervention period, it was a bit challenging to ensure that each participant had the right progression throughout the three intervention periods according to the study protocol. Therefore, shared decision making between the participant and the local physical therapist to gradually increase exercise intensity was of high importance in this first project of HIT in the *de novo* HTx recipients. A close dialogue between the local physical therapist and the in-hospital therapist (HITTS collaborator) was also useful for discussing progress in both the RPE and the changing (improving) heart rate.

6.5 Cardiopulmonary exercise testing treadmill versus bicycle

CPET with measurement of VO_{2peak} is the preferred method for quantifying exercise capacity (34). A CPET is usually performed on a treadmill or an ergometer bicycle (202). These two test modalities have some important differences to consider. Walking is a more common activity than bicycling, and a larger amount of muscle mass is used against gravity when walking on a treadmill, generating a higher stress on the cardiovascular and the peripheral

organ systems. The $VO_{2\text{peak}}$ is reported to be 5–10% higher on a treadmill compared to a bicycle (203). On the other hand, it is easier to measure blood pressure and electrocardiogram on a bicycle, which is more stable and generates less disturbance. In the HITTS study, the primary endpoint was $VO_{2\text{peak}}$ and the test was also used to determine the intensity of the exercise intervention, therefore a treadmill test was the preferred method. However, bicycle testing was used if participants had orthopedic issues that made it difficult to walk on a treadmill. An ergometer bicycle was also used by all the participants from Gothenburg and Copenhagen, since bicycle testing is the standard method in those centers. The average $VO_{2\text{peak}}$ per group is probably a bit affected and lower than expected because 11 of the participants were tested on a bicycle, but because the primary endpoint was the mean change in $VO_{2\text{peak}}$, the different test modalities has not impacted the results

6.6 Variables measured at rest

In the HITTS study both the echocardiography and the right heart catheterization were measured at rest, which is a major limitation for detecting effects of an exercise intervention on cardiac function. A-v O_2 diff, was as earlier mentioned also calculated from values measured at rest (cardiac output and VO_2). If these measurements had been performed at peak exercise, we might had detected any true changes that might have occurred in left ventricle function and the a-v O_2 diff.

6.7 Isokinetic muscle strength testing

Muscle strength testing using isokinetic devices is common in rehabilitation and research (204, 205). The advantages of this method are the standardization and the ability to test specific muscle groups at different angle positions, both eccentric and concentric (205). In the

HITTS study (Papers 1 - 3), the three study centers used different isokinetic devices, but the same standardized test protocol was used (as described in the “Materials and methods”). In addition, all the three devices used in the study — the Cybex 6000 (110), the Kinetic Communicator (112, 206) and the IsoMed2000 (113) — have been tested for validity and reliability.

The disadvantages of using such a method in daily clinical practice are that the devices are expensive and trained test personnel are needed for them to be used properly (205). The 30 seconds sit- to- stand test might be an alternative method for measuring muscle strength in the lower limbs (207). This method has shown to correlate moderately with isokinetic muscle strength measurements (Cybex 6000) in participants with musculoskeletal conditions (208). The implementation of a method for systematic strength testing in clinical practice is relevant for the HTx population. For this reason, we could have considered to use the 30 seconds sit-to-stand test in the HITTS study, since the test probably would be more feasible for use in clinical practice than the isokinetic device. However, one of the main reasons to choose the isokinetic device method in the HITTS study, was the ability to compare the results from the *de novo* HTx recipients with results from previously studies in our research group using isokinetic that used this method of muscle strength testing in maintenance HTx recipients (23, 25, 111).

6.8 Health-related quality of life questionnaires

When measuring HRQoL after HTx, questionnaires designed for reporting specific transplant-related issues as well as general health concerns are preferred (209).

In the HITTS study, we only used a generic questionnaire (SF-36v2) because no HTx specific questionnaire is available in Norwegian. We could have used a heart disease specific

questionnaire, like the Kansas City Cardiomyopathy questionnaire (KCCQ) (210), which has been used in earlier studies with HTx recipients (211-214). Our experience with the KCCQ from an earlier study is that the HTx recipients found it somewhat confusing to answer questions about heart failure after they had had a HTx. The same observations have been reported by Emin et al. (212). We therefore decided not to use KCCQ in the HITTS study. However, only using generic questionnaires when investigating HRQoL after HTx is a limitation because the generic questionnaires have a lower sensitivity than disease-specific HRQoL questionnaires (84), and these questionnaires will probably not be able to detect certain changes over time that pertain especially to HTx (209).

6.9 Measuring exercise at the 3-year follow-up

In the 3-year follow-up study (Paper 4), we reported the sustainability of HIT based on the intensity of physical activity reported by the questionnaire (adapted from HUNT3) and the intensity of the daily physical activity observed by the SenseWear Armband Mini. In retrospect, specific questions about the exercise habit of the participants after the intervention (intensity, frequency and types of exercise, e.g. whether HIT or MICT) should have been included, and the absence of such questions is a limitation of the study.

6.10 Lack of a non-exercising control group

One major limitation in the HITTS study is the lack of a non-exercising group. Since all newly HTx patients are enrolled into a general cardiac rehabilitation program, it was not ethically acceptable to include a third non-exercising group in this study. If patients had been included > 1 year after the transplantation, a non-exercising group could have been considered. After one year, the participants have already undergone the initial exercise-based

cardiac rehabilitation program and are encouraged to maintain physical activity and exercise on their own. However, it will always be an ethical challenge to advise HTx patients not to exercise at any time-point after a transplantation.

6.11 Non-blinded study

One of the limitations of doing an exercise study is the non-blinded design. It is impossible to blind the participants and the supervisors for the given intervention. Another aspect is the blinding of study personnel for collecting the data, which is important where subjects might be affected by encouragement given by the tester, for instance, when doing CPET and strength testing (215). In the HITTS study, we were aware of this potential bias. At baseline both the participants and study personnel performing the exercise tests were blinded — the envelope with the group randomization was opened after the tests. At the follow-up tests, however, allocation to group was known. One solution to this potential bias could be to engage personnel not involved in the study to perform the exercise tests (215). This suggestion is however often not practical or possible in a busy hospital setting. In the HITTS study, we were conscious about giving the exact same encouragement to all the participants both at baseline and at follow-up tests.

6.12 Multicenter trial design

In the planning of the HITTS trial, our goal was to include more recipients from the cooperating centers in Sweden (Sahlgrenska University Hospital) and Denmark (Rigshospitalet), as described in the design article (106). Unfortunately, due to fewer transplantations than expected at the cooperating centers, most of the participants in the HITTS 1-year follow-up were from Norway (Oslo University Hospital). In the 3-year follow-

up study, only the Norwegian cohort was included. The generalizability of our study is weakened due to these circumstances.

7 Ethical considerations

The HITTS trial was approved by the South-East Regional Ethics Committee in Norway [number 2012/2305] and the local Data Protection Officer at Oslo University Hospital [number 2013/2496], the Regional Ethics Review Board in Gothenburg (Sweden) [number 835-14] and the Scientific Research Ethics Committee for the Capital Region of Denmark (Copenhagen) [number H-3-2014-106].

The study is registered at the ClinicalTrials.gov [Identifier NCT01796379 <https://clinicaltrials.gov/ct2/show/NCT01796379>] and was done according to the Declaration of Helsinki (216).

All participants were given written and oral information about the study and gave their written, informed consent before inclusion.

Safety is an important part of the ethical considerations in research. The HITTS study was the first trial with HIT with recent HTx participants and the safety perspective was always first. Participants went through a medical examination and were informed about all the test procedures in the study and the potential risks. Before starting the intervention, participants in both groups were thoroughly informed about the exercise intervention and informed about the importance of reporting any symptoms or discomfort they might experience during or after the exercise sessions. The local physical therapists were also well informed about both general principles of exercise after HTx as well as the study intervention. Participants were monitored during every session, and the HIT group were told not to do HIT sessions alone. Both local physical therapists and participants had a direct line to the study personnel and were encouraged to call immediately if anything unexpected happened during exercise.

The HITTS study was an open prospective randomized study investigating the effect of two different exercise interventions. We put great effort into giving the same attention to both groups, as per protocol.

We have, as far as possible, tried to include all newly HTx participants, regardless of age, gender and starting point. However, due to the intervention type, the sickest patients could not be included, and this might be a risk for the generalizability of the study results.

8 Main conclusions

1. Important predictors of VO_{2peak} in the early phase after HTx seem to be both central and peripheral factors.

2. A. High-intensity interval training (HIT) was shown to be a safe and effective exercise method at 1-year follow-up.

B. The mean difference in VO_{2peak} between HIT and moderate intensity continuous training (MICT) groups was 1.8 mL/kg/min higher in the HIT group. Additionally, the HIT group had significantly better muscular exercise capacity, peak expiratory flow and higher AT.

C. Within-group analyses showed that the MICT group also had significant improvements in VO_{2peak} , confirming the known benefits of the common cardiac rehabilitation program.

3. Both groups had similar significant increases in the physical domains of HRQoL, with stable and high mental components of HRQoL throughout the intervention period

4. A. After 3 years, the statistically significant mean difference in VO_{2peak} between the two groups seen at 1-year was not sustained.

B. The HIT group still had a significantly better muscular exercise capacities of the extensors and significantly higher AT, suggesting some long-lasting effects of HIT.

C. HRQoL scores were high in both groups three years after HTx.

8.1 Clinical implications and future perspectives

There are several clinical implications of this study. First, the great value of systematic exercise-based rehabilitation in the early phase after HTx must be underscored. New HTx recipients are particularly deconditioned with a severely reduced VO_{2peak} (7, 45). Decreased VO_{2peak} and self-reported physical function is associated with reduced long-term survival (4).

Thus, improved exercise capacity is an important goal in the early post-HTx rehabilitation program (217). The importance of an early intervention is further underscored in a study showing that the number of attended cardiac rehabilitation sessions during the first 90 days after HTx was a predictor of long-term survival (145). The exercise capacity improvements after cardiac rehabilitation in maintenance HTx recipients has been shown to be quickly lost when patients stop exercising (26). Therefore, early, and systematic exercise routines after HTx may contribute to good and life-long physical activity habits. Decentralized exercise training as used in the HITTS study facilitates a longer duration of the rehabilitation program and a closer follow-up, both of which increase the chances for future adherence. A variety of exercises are often more enjoyable and will keep the patient motivated longer. Thus, both HIT and MICT activities should be emphasized for achieving a long-lasting, healthy and active lifestyle. HIT and MICT can be adapted to several different physical activities, such as skiing, rowing, swimming, dancing and walking. HTx recipients are a heterogeneous population, and an individually tailored exercise prescription for each HTx recipient's specific needs and interests is crucial. The HITTS study has shown that HIT is safe and can be prescribed in the early phase after HTx in medically stable recipients. However, HIT is maybe not the preferred method for exercise for every HTx recipient in this early phase. For the first six months, MICT is probably good enough exercise for most of the HTx recipients. After six months, systematic HIT seems to be easier to conduct and will presumably also be more effective at that time. However, implementing HIT on a regular basis in the longer term after HTx is still a question of concern. Future research should study the effects of different HIT protocols with either interval bouts of shorter duration or HIT with fewer repetitions, since 4 times x 4 min as per protocol in the HITTS study seem to be too demanding for the average HTx recipient. If the same effects are gained with shorter interval bouts or with fewer repetitions, maybe

more patients will be motivated to adhere to this form for strenuous exercise in the longer term.

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Papers 1 - 4

Effect of High-Intensity Interval Training in De Novo Heart Transplant Recipients in Scandinavia

One-Year Follow-Up of the HITTs Randomized, Controlled Study

Editorial, see p 2212

BACKGROUND: There is no consensus on how, when, or at what intensity exercise should be performed after heart transplantation (HTx). We have recently shown that high-intensity interval training (HIT) is safe, well tolerated, and efficacious in the maintenance state after HTx, but studies have not investigated HIT effects in the de novo HTx state. We hypothesized that HIT could be introduced early after HTx and that it could lead to clinically meaningful increases in exercise capacity and health-related quality of life.

METHODS: This multicenter, prospective, randomized, controlled trial included 81 patients a mean of 11 weeks (range, 7–16 weeks) after an HTx. Patients were randomized 1:1 to 9 months of either HIT (4×4-minute intervals at 85%–95% of peak effort) or moderate-intensity continuous training (60%–80% of peak effort). The primary outcome was the effect of HIT versus moderate-intensity continuous training on the change in aerobic exercise capacity, assessed as the peak oxygen consumption (Vo_2peak). Secondary outcomes included tolerability, safety, adverse events, isokinetic muscular strength, body composition, health-related quality of life, left ventricular function, hemodynamics, endothelial function, and biomarkers.

RESULTS: From baseline to follow-up, 96% of patients completed the study. There were no serious exercise-related adverse events. The population comprised 73% men, and the mean±SD age was 49±13 years. At the 1-year follow-up, the HIT group demonstrated greater improvements than the moderate-intensity continuous training group; the groups showed significantly different changes in the Vo_2peak (mean difference between groups, 1.8 mL·kg⁻¹·min⁻¹), the anaerobic threshold (0.28 L/min), the peak expiratory flow (11%), and the extensor muscle exercise capacity (464 J). The 1.8-mL·kg⁻¹·min⁻¹ difference was equal to ≈0.5 metabolic equivalents, which is regarded as clinically meaningful and relevant. Health-related quality of life was similar between the groups, as indicated by results from the Short Form-36 (version 2), Hospital Anxiety and Depression Scale, and a visual analog scale.

CONCLUSIONS: We demonstrated that HIT was a safe, efficient exercise method in de novo HTx recipients. HIT, compared with moderate-intensity continuous training, resulted in a clinically significantly greater change in exercise capacity based on the Vo_2peak values (25% versus 15%), anaerobic threshold, peak expiratory flow, and muscular exercise capacity.

CLINICAL TRIAL REGISTRATION: URL: <https://www.clinicaltrials.gov>. Unique identifier NCT01796379.

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Key Words: exercise test ■ heart transplantation ■ high-intensity interval training ■ muscle strength ■ peak oxygen consumption ■ health-related quality of life ■ safety

Sources of Funding, see page 2209

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Clinical Perspective

What Is New?

- This randomized, controlled trial was the first to show that the effect of 9 months of high-intensity training in de novo recipients of heart transplants produced a clinically meaningful, significantly larger increase in peak oxygen consumption and muscular exercise capacity compared with moderate-intensity continuous training.
- This unique, cost-effective intervention was decentralized and conducted in cooperation with primary healthcare services; the one-on-one intervention in both groups contributed to high adherence and high completion rates.

What Are the Clinical Implications?

- This novel project and the advanced measurements demonstrated that exercise training is effective in most patients with heart transplantation and should start shortly after transplantation.
- High-intensity training is feasible in the de novo patients with heart transplantation and is more effective than the current moderate-intensity training program.
- Exercise training can easily be implemented and performed while supervised by local physiotherapists close to the patient's home instead of in more resource-demanding in-hospital rehabilitation programs.

Hearth transplantation (HTx) is an established treatment for end-stage heart disease. Despite the improvement that HTx offers in hemodynamic status, these patients have higher morbidity rates and lower life expectancy,^{1,2} health-related quality of life (HRQOL),³ and functional capacity^{3,4} compared with healthy subjects. These limitations result mainly from the development of early and late complications caused by the side effects of immunosuppressive medications.^{1,5} Thus, there is a need to improve well-being and survival in HTx recipients.

A prominent limitation after HTx is impaired exercise tolerance, measured objectively as a reduction in peak oxygen consumption (Vo_2peak). Previous studies have shown that Vo_2peak was reduced by $\approx 70\%$ compared with age-matched healthy control subjects,⁴ secondary to both central and peripheral factors.^{6,7} Reduced exercise tolerance was associated with reduced survival⁸ and reduced HRQOL^{9,10}; thus, improving exercise capacity is a major goal after HTx. Exercise is an essential part of most rehabilitation programs after HTx, but surprisingly few randomized studies have studied the effects of this intervention.^{3,11–13} Of those conducted, most have used traditional moderate training, which resulted in only a moderate increase in the Vo_2peak .^{3,4,7,11,12}

Previous studies have reported that high-intensity training (HIT) was superior to moderate-intensity continuous training (MICT) in improving exercise capacity in healthy subjects¹⁴ and in patients with different cardiovascular disorders.^{15–17} MICT induced several health benefits, similar to those induced by HIT, but HIT had a superior effect, particularly related to stroke volume.¹⁴ A clear exercise-related effect on stroke volume remains to be studied in HTx recipients.^{18,19}

We have recently demonstrated that HIT is safe, well tolerated, and efficacious in HTx recipients who are in maintenance status.^{20–24} However, to date, no studies have investigated the effects of HIT in de novo HTx recipients. One reason for this has been a concern that HIT might induce adverse effects as a result of the denervated state of the transplanted heart. However, we and others have demonstrated that, during the first year after HTx, partial reinnervation takes place, and the heart rate (HR) response to exercise is nearly normalized. This reinnervation might explain the tolerability to HIT exercise in the maintenance HTx state.^{4,7,25} In contrast, the newly transplanted heart is denervated; consequently, the HR response is greatly reduced compared with healthy subjects. Moreover, studies have shown that different factors are predictive of Vo_2peak in HTx recipients, depending on the time they are measured after an HTx. For example, in the first months after an HTx, both central factors (ie, stroke volume and chronotropic responses) and peripheral factors seem to be predictive of Vo_2peak ; however, later on, peripheral factors (ie, muscular strength and function) are the dominant predictive factors.^{6,26–28}

Although in the early phase after HTx central factors might be the leading cause of reduced Vo_2peak , de novo HTx recipients are also frequently physically deconditioned, with low muscular capacity, because of their heart failure history. This state is likely to contribute additionally to a reduced Vo_2peak .²⁹ Thus, we hypothesized that HIT could be safely introduced early after surgery and that it would result in clinically meaningful increases in exercise capacity and HRQOL. We tested this hypothesis in a multicenter, prospective, randomized trial to test HIT versus MICT treatments in de novo HTx recipients.³⁰

METHODS

The data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure because of our strict policies for data sharing and privacy protection.

Study Design

The main design of the HITS study (High-Intensity Interval Training in Heart Transplant Recipients in Scandinavia) has been described previously.³⁰ In short, the HITS 1-year follow-up study was a prospective, 2-arm, multicenter clinical study

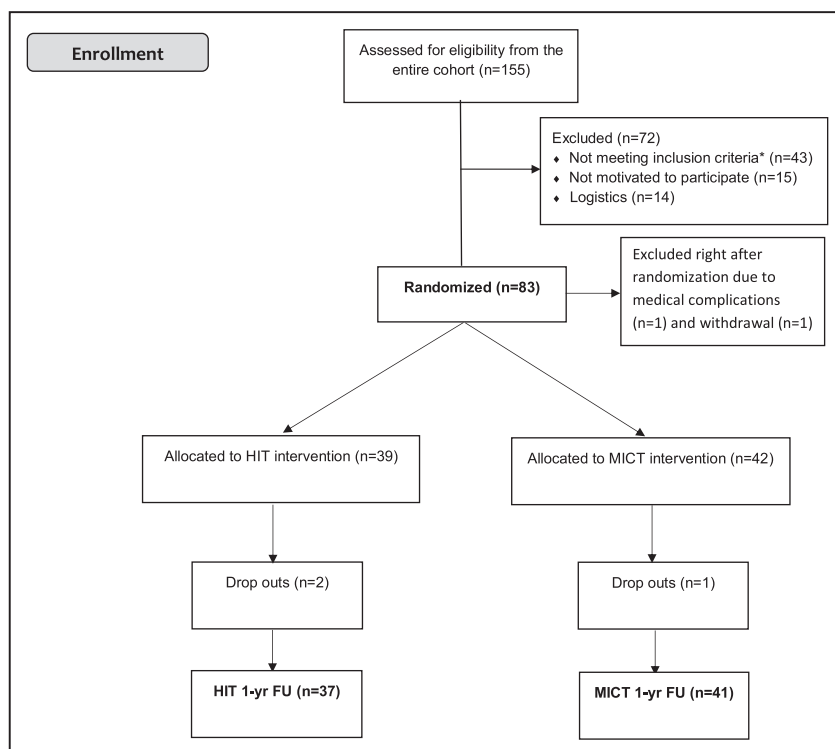


Figure 1. Flowchart.

FU indicates follow-up; HIT, high-intensity interval training; and MICT, moderate-intensity continuous training. *Reasons for not meeting inclusion criteria (n=43) were cognitive issues (n=4), physical disabilities (n=3), medical complications (n=24), language barriers (n=3), contagion (n=2), no physical therapist available (n=5), and multiorgan transplantation (n=2).

that enrolled de novo HTx recipients. The collaborating centers were Copenhagen, Gothenburg, and Oslo; Oslo served as the core center. Included patients were randomized in a 1:1 allocation to either HIT or MICT (Figure 1). The intervention period for both groups started \approx 3 months after HTx and lasted for 9 months up to the follow-up testing at 1 year after HTx.

Patients

For inclusion, patients had to be clinically stable, >18 years of age, and receiving immunosuppressive therapy according to local protocols (Table 1 in the online-only Data Supplement). Patients also had to be willing and able to give written informed consent for study participation and motivated to participate in the study for 9 months. Patients were enrolled (after providing written informed consent) 6 to 8 weeks after surgery. Baseline testing was performed after inclusion at a mean of 11 weeks (range, 7–16 weeks) after HTx. Allocation to the exercise group was not revealed to study subjects or study personnel until after baseline tests had been performed. At the follow-up exercise tests, all investigators were encouraged to use similar instructions and motivational phrases regardless of the exercise group to which the participant belonged.

Intervention

Patients from both groups were supervised and followed up in the same manner. Each patient was given general advice about lifestyle changes, including a healthy diet, regular exercise, no smoking, and how to avoid infections. For exercise, they were followed up in the primary healthcare setting in their local communities by local physical therapists, in a 1:1 setting, at the physical therapist's facilities (81 participants in 77 different locations). Each therapist was frequently in contact with the main research center via email and telephone.

According to protocol, all patients were advised to exercise 2 to 3 times per week during the intervention period; at that rate, each patient would perform a total of \approx 72 supervised exercise sessions, and each session was planned to last \approx 40 minutes (both groups; Figure 2). Thus, the only difference in protocol between the groups was the intensity of the exercise. All patients in both groups were provided with a Polar FT1 HR monitor (Polar Electro Oy, Kempele, Finland). A detailed description of the 2 intervention arms is presented in Table II in the online-only Data Supplement.

High-Intensity Training

The HIT intervention consisted mainly of 2- to 4-minute intervals at 85% to 95% of peak effort (85%–95% of peak HR or \approx 81%–93% of V_{O_2} peak). This intensity corresponded to a rating of perceived exertion of 16 to 18 (according to the Borgs scale; Figure 2A). The 9-month intervention was divided into 3 main periods, and the HIT protocol became progressively more difficult (increases in interval lengths and intensities) in each period, as previously described.³⁰ Briefly, the first period (3–6 months after HTx) consisted of 1 HIT session, 1 resistance training session (core musculature and large muscle groups), and 1 combined session per week. The second period (6–9 months after HTx) consisted of 2 HIT sessions and 1 resistance training session (the last with or without supervision) per week. The last 2 to 3 months of the intervention (up to the first annual follow-up at 12 months after HTx) consisted of 3 HIT sessions per week. All the sessions were supervised and logged by the physical therapists, who recorded the exercise frequency, duration, and intensity (data from the HR monitor).

Moderate-Intensity Continuous Training

The control group performed the same amount of supervised physical activity (2–3 times per week) but followed standard care procedures consisting of MICT, which was performed at

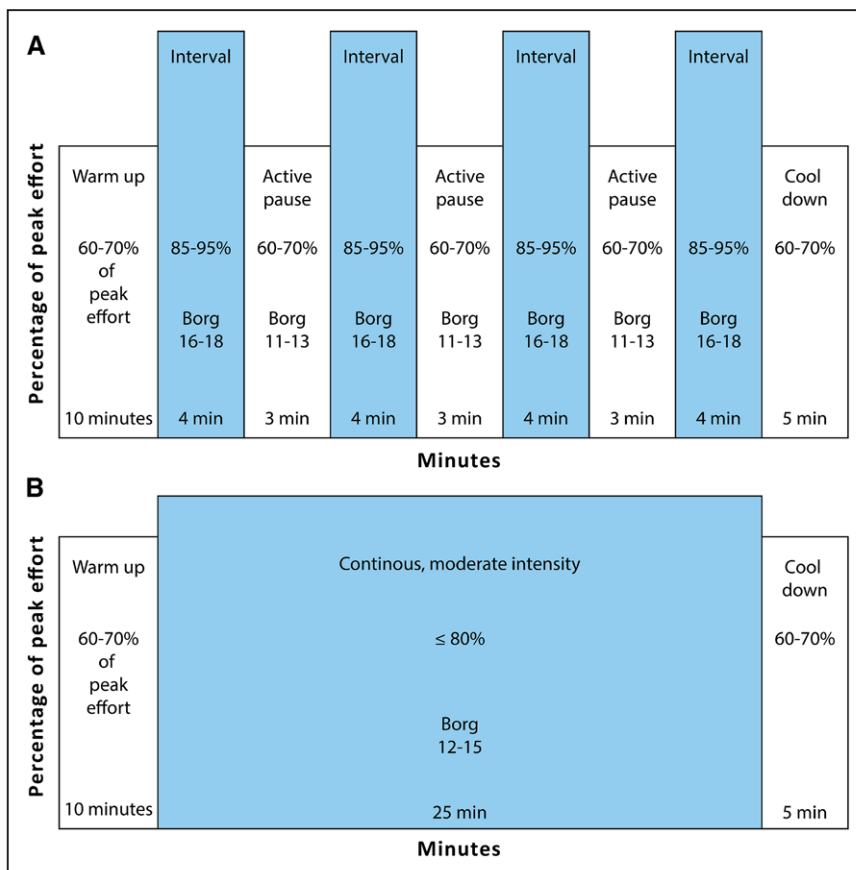


Figure 2. Illustration of the 2 exercise protocols: a session of (A) high-intensity interval training and (B) moderate-intensity continuous training.

This figure has previously been published in *Am Heart J.* 2016;172:96–105. Reproduced with permission (<https://www.sciencedirect.com/science/article/pii/S0002870315006286>).

60% to 80% of peak effort (Figure 2B), regular core strengthening exercises, and exercises for large muscle groups. Like the HIT intervention, all sessions were supervised and carefully monitored. The physical therapists logged the exercise type, frequency, duration, and intensity. They also recorded the maximum and mean HR and rating of perceived exertion (Borg scale) in each session.

Adherence was measured continuously. For each patient, the number of supervised sessions was recorded weekly throughout the intervention period. There was close and regular contact, via email and telephone, between the in-hospital physical therapist and the local physical therapists and between the local physical therapist and the patient. Per protocol, the in-hospital physical therapist had a face-to-face consultation with all patients at 6 months after HTx. In addition, all patients were invited to call the in-hospital physical therapist to discuss any problems or questions.

Outcomes

The primary end point was the change in $\dot{V}O_{2peak}$ from baseline to follow-up, and the mean change was compared between groups. Secondary and exploratory outcomes conducted at baseline and at 12 months after HTx included muscular capacity, measured as the maximum muscular strength and muscular exercise capacity; chronotropic responses; right-sided heart catheterization hemodynamics; lung function; cardiac dimension and function, assessed with echocardiography; arteriovenous oxygen difference (a-v O_2 diff); endothelial function; HRQOL; tolerability; safety; and exercise-related

adverse events. All study end points were read and controlled by personnel who were blinded for the intervention.

Cardiopulmonary Exercise Test

The cardiopulmonary exercise test was performed a mean of 11 weeks (range, 7–16 weeks) after HTx on either a treadmill (Norway) or a bicycle ergometer (Sweden, Denmark). The criteria for passing the test were a respiratory exchange ratio ≥ 1.05 for the treadmill and ≥ 1.10 for the bicycle ergometer test. For both tests, a passing Borg scale score was > 18 . The other equipment and protocols used were described previously.³⁰

Muscular Strength

Muscle strength was measured in the lower limbs; both extensors and flexors were measured isokinetically. As previously described,³⁰ the 3 centers used different instruments, but each patient used the same instrument at baseline and follow-up. Overall, maximal strength was measured as the mean value of 5 repetitions at a low angular velocity ($\approx 60^\circ/s$; Newton meter), and muscular exercise capacity was the sum (joules) of 30 repetitions at a high angular velocity ($240^\circ/s$).

Hemodynamics, Echocardiography, and Endothelial Function

Right-sided heart catheterization was performed as described by Gude et al.³¹ Standard Doppler echocardiography was performed by experienced technicians and assessed by

Table 1. Baseline Clinical Characteristics in the HIT and MICT Groups

Variables	HIT (n=37), Mean±SD	MICT (n=41), Mean±SD	P Value
Male, n (%)	28 (76)	29 (71)	0.623*
Age, y	50±12	48±14	0.675
Primary diagnosis, n (%)			
CM/CAD/other	21(57)/14(38)/2(5)	31(75)/6(15)/4(10)	0.069†
Donor age, y	37±14	39±14	0.643
Ischemic time, min	181±77	184±82	0.869
Rejections‡ grade 1–2, n (%)	15 (41)	20 (50)	0.405
CMV serology before HTx, n (%) positive	28 (76)	22 (55)	0.057*
Exercise testing, wk after HTx	11±2	11±2	0.674
Time with HF before HTx, y	6±6	6±5	0.884
Time on HTx wait list, d	153±215	143±238	0.841
Smoking, yes/no (ex-smoker), n (%)	18 (49)/19 (51)	21 (51)/20 (49)	0.821*
Medication at inclusion, n (%)			
Cyclosporine	24 (65)	31(76)	0.299*
Tacrolimus	11(30)	10 (24)	0.596*
Everolimus	12(32)	13 (32)	0.945*
Prednisolone	37 (100)	41 (100)	
Mycophenolate	34 (92)	36 (88)	0.715†
Statins	36 (97)	41 (100)	0.481†
β-Blocker	9 (24)	12 (30)	0.576*
Calcium blocker	8 (22)	12 (30)	0.402*
ACE inhibitor	0	2 (5)	0.494†
ARB inhibitor	4 (11)	3 (8)	0.708†
Diuretics	31 (84)	32 (78)	0.520 *

ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CAD, coronary artery disease; CM, cardiomyopathy; CMV, cytomegalovirus; HF, heart failure; HIT, high-intensity interval training; HTx, heart transplantation; and MICT, moderate-intensity continuous training.

*By χ^2 test.

†By Fisher exact test.

‡Rejections correspond to the International Society for Heart and Lung Transplantation grade 1 or 2 before baseline testing.

cardiologists to determine myocardial size and function. Endothelial function was assessed by brachial artery flow-mediated dilatation and the fingertip reactive hyperemia index. The EndoPat apparatus was described by Dahle et al.³² The echocardiography and right-sided heart catheterization were performed as clinical routine (performed by different clinicians), and the clinicians were blinded to the randomization, including the single clinician who performed the EndoPat.

a-v O₂ Diff

The a-v O₂ diff was calculated according to the Fick equation and was based on the resting Vo₂ values from the cardiopulmonary exercise test and cardiac output measurements acquired during right-sided heart catheterization.

Lung Function

Different lung function variables were measured both at rest and during exercise. Spirometry was performed at rest before the cardiopulmonary exercise test to obtain the peak expiratory flow, forced expiratory volume at 1 second (FEV₁), and forced vital capacity. During exercise, the maximum ventilation and ventilatory efficiency were calculated.

Health-Related Quality of Life

HRQOL was measured with the generic questionnaire Short Form-36, version 2. Unlike a disease-specific questionnaire, a generic HRQOL questionnaire can be used in the healthy population and in specific patient populations.³³ Subscales were aggregated into 2 summed scores: the Physical Component Summary and the Mental Component Summary. Scores were transformed to norm-based scores with a mean of 50±10.³³ Symptoms of anxiety and depression were measured with the generic Hospital Anxiety and Depression Scale.³⁴ In addition, the patients rated usefulness and their overall satisfaction of the intervention on a visual analog scale.

Approval and Ethics

This study was approved by the South-East Regional Committee for Medical and Health Research Ethics in Norway and the Committee for Medical and Health Research Ethics in Sweden and Denmark. This study was conducted in accordance with recommendations in the Helsinki Declaration. This study was registered at <http://www.clinicaltrials.gov> (identifier, NCT01796379). All participants provided written informed consent before inclusion in the study.

Statistical Analysis

All data were analyzed with IBM SPSS, version 25.0 (IBM Corp). Continuous data are expressed as the mean±SD or the median and interquartile range. Categorical data are presented as percentages. Within-group comparisons were performed with paired-samples *t* tests and the Wilcoxon signed-rank test. Comparisons of the mean changes between groups were performed with an independent-samples *t* test or Mann-Whitney *U* test as appropriate. Baseline-adjusted ANCOVA tests were also performed for verification of and comparison with the *t* test analyses (Table III in the online-only Data Supplement). The χ^2 or Fisher exact test was used for comparing categorical data.

Clinically relevant predictors (age and sex) and other potential explanatory variables, based on a statistically significant ($P<0.05$) association with the dependent variable on univariate analyses, were included in the multiple regression analysis to identify the degree of association with the mean difference in Vo₂peak. The final model was built with a series of multiple regression analyses, performed with the enter method (forced entry). Assumptions were checked for normality and linearity, and none of the models were overfitted with respect to the total number.

We also performed a multiple regression analysis to compare previously published baseline predictors²⁸ with the Vo₂peak level at follow-up. As described previously,³⁰ the power calculation was based on an estimated mean Vo₂peak difference between groups of 3 mL·kg⁻¹·min⁻¹, an SD of 5 mL·kg⁻¹·min⁻¹, an α of

Table 2. Change in the Main Exercise-Related Variables From Baseline to Follow-Up in the HIT and MICT Groups and Comparisons Between Groups

Variables	HIT (n=37), Mean±SD		MICT (n=41), Mean±SD		Mean Difference Between Groups (95% CI)	P Value, t Test
	HIT Baseline	HIT 1-y Follow-up	MICT Baseline	MICT 1-y Follow-up		
Exercise/CPET						
Vo ₂ peak, mL·kg ⁻¹ ·min ⁻¹	19.5±4.3	24.4±6.5*	21.3±5.3	24.4±6.7*	1.8 (0.1 to 3.5)	0.044
Improvement in mL·kg ⁻¹ ·min ⁻¹ , %		25.2±21.1		15.1±17.8	10.1 (1.3 to 19.0)	0.025
Percent of predicted Vo ₂ peak	53±12	67±15*	58±13	67±15*	5 (0 to 9)	0.040
Vo ₂ peak, L/min	1.51±0.40	2.03±0.57*	1.65±0.44	1.97±0.58*	0.20 (0.04 to 0.36)	0.014
Respiratory exchange ratio	1.17±0.11	1.19±0.09	1.22±0.13	1.22±0.09	0.02 (−0.03 to 0.07)	0.338
Borg scale score	18.7±0.5	18.8±0.6	18.5±1.1	18.8±0.7	0.2 (−0.3 to 0.7)	0.424
Test duration, min	9.1±2.2	14.6±4.2*	9.8±3.1	13.1±4.3*	2.2 (0.7 to 3.7)	0.005
O ₂ pulse, mL/beat	11.8±3.2	13.1±3.3*	13.1±3.4	13.6±3.9	0.9 (−0.1 to 1.9)	0.081
V _{emax} , L	68.8±20.9	87.0±29.4*	74.7±24.4	85.3±29.0*	7.5 (−0.7 to 15.8)	0.074
V _E /V _{CO₂} slope	35.2±8.3	31.5±5.5†	34.5±7.5	29.2±5.3*	−1.6 (−5.2 to 2.0)	0.375
AT, L/min	1.01±0.27	1.44±0.51*	1.14±0.36	1.28±0.50†	0.27 (0.09 to 0.46)	0.004
AT at percent of Vo ₂ peak	67.7±13.3	70.0±12.2	70.0±12.7	65.5±12.0	6.8 (−1.7 to 15.2)	0.135
Chronotropic responses						
Peak HR, bpm	128±17	153±18*	127±21	147±22*	5 (−2, 12)	0.129
HR maximum, %	75±12	90±12*	74±13	86±12*	4 (0 to 8)	0.078
HR reserve, bpm	42±15	65±19*	44±16	62±21*	5 (−4 to 14)	0.280
Chronotropic response index	0.51±0.19	0.82±0.24*	0.52±0.21	0.75±0.24*	0.08 (−0.01 to 0.18)	0.090
HRR, beats at 2 min	−1±4	−19±12*	0±6	−17±13*	0 (−5 to 6)	0.866
Muscular capacity						
Maximal muscle strength extensors, Nm	184±74	237±81*	186±73	222±80*	18 (−3 to 39)	0.094
Muscular exercise capacity extensors, J	2154±952	3170±1267*	2319±1201	2870±1240*	464 (63 to 863)	0.024

AT indicates anaerobic threshold; bpm, beats per minute; CPET, cardiopulmonary exercise test; HIT, high-intensity interval training; HR, heart rate; HRR, heart rate recovery; J, joule; MICT, moderate-intensity continuous training; Nm, Newton meter; V_{CO₂}, carbon dioxide production; V_E, ventilation; and V_{emax}, maximum ventilation.

*P<0.001.

†P<0.05 within group.

5%, and a power of 80%. The analysis indicated that at least 44 patients were required in each group. Because fewer HTxs were performed than expected at our collaborating centers during the inclusion period and as a result of logistic problems, the final analysis included a total of 81 patients.

RESULTS

A total of 155 de novo HTx were assessed for eligibility during the inclusion period, from 2013 to 2017. As illustrated in the flowchart in Figure 1, 74 patients were excluded for various reasons. Eighty-one were tested at baseline, and 3 dropped out during the intervention period. Thus, 78 patients successfully completed the 1-year follow-up: 37 in the HIT group and 41 in the MICT group. The 2 dropouts in the HIT group were the result of 1 hospitalization (due to nose- and throat-related issues), and 1 who did not comply with the exercise protocol and chose to withdraw from the study. In the MICT group, 1 patient dropped out because of a brain arteriovenous malformation (Figure 1).

Clinical Characteristics

Among the total study population (n=78), the mean±SD age was 49±13 years, and men made up 73% of the cohort. Baseline testing was performed at 11±2 weeks after HTx. The clinical characteristics are presented in Table 1 according to group. Although the baseline Vo₂peak was numerically lower in the HIT group at baseline (Table 2), the difference between groups was not significant. All baseline variables in Tables 1 through 3 were tested for between-group differences. The only significant difference in baseline characteristics between the 2 groups was the 24-hour overall HR (Table 3).

Compliance, Safety, and Adverse Events

Both the HIT and the MICT groups (n=78) performed a mean±SD of 58±22 exercise sessions during the 9-month intervention. Thus, of the initially planned 72 exercise sessions, 81% was accomplished. In the HIT group, the mean exercise session length increased from the first to

Table 3. Change in Secondary and Exploratory Variables From Baseline to Follow-Up in the HIT and MICT Groups and Comparisons Between Groups

Variables	HIT (n=37), Mean±SD		MICT (n=41), Mean±SD		Mean Difference Between Groups (95% CI)	P Value, t Test
	HIT Baseline	HIT 1-y Follow-up	MICT Baseline	MICT 1-y Follow-up		
Spirometry						
PEF, %	82±22	93±19*	90±23	89±22	11 (2 to 20)	0.020
FEV ₁ , %	77±14	86±17*	86±18	92±18*	2 (−2 to 7)	0.274
a-v O ₂ diff at rest (pretest), mL	5.1±2.0	6.1±1.7†	5.6±2.4	6.0±2.0	0.7 (−0.5 to 1.9)	0.227
Blood pressure, mm Hg						
24-h overall SBP	131±9	139±12*	134±13	135±15	6 (−1 to 12)	0.071
24-h overall DBP	80±5	85±7*	82±8	83±9	4 (0 to 7)	0.045
24-h overall HR‡	91±9	93±10	86±10	91±10†	−3 (−7 to 1)	0.208
Body composition						
Weight, kg	78.4±14.0	84.4±16.1*	78.3±15.4	79.6±17.8	4.4 (−0.3 to 9.2)	0.068
Body mass index, kg/m ²	24.8±3.4	26.8±4.0*	25.6±3.9	26.6±4.2*	0.9 (0.0 to 1.8)	0.048
Body fat, %	24.2±7.9	26.4±8.5†	26.0±9.5	25.8±9.8	2.4 (0.1 to 4.7)	0.043
Muscle mass, kg	55.1±9.7	58.0±11.5*	54.6±11.1	57.0±11.6*	0.5 (−1.2 to 2.1)	0.571
Biomarkers						
Hemoglobin, g/dL	11.8±1.8	12.9±1.5*	11.7±1.6	12.6±1.7*	0.2 (−0.4 to 0.9)	0.471
Creatinine, μmol/L	116±34	102±23*	119±28	104±28*	−0.1 (−12 to 12)	0.984
eGFR, mL·min ^{−1} ·1.73 m ^{−2}	65±21	74±21†	63±23	73±26*	−2 (−10 to 6)	0.605
hs-CRP, median (IQR), mg/L	2.7 (4)	2.0 (6.9)	1.9 (5.6)	1.9 (3.2)		0.932§
hs-troponin T, median (IQR), ng/L	31.5 (46.3)	14.9 (12.5)*	34.0 (42.5)	13.5 (20.8)*		0.584§
NT-proBNP, median (IQR), ng/L	1019 (1259)	372 (396)*	947 (884)	249 (311)*		0.641§
Echocardiography						
HR at rest (during echocardiography), bpm	88±8	90±11	85±10	87±11	0 (−4 to 4)	0.875
Ejection fraction, %	56.7±5.3	56.0±6.2	58.6±5.8	58.8±7.0	−1.0 (−4.4 to 2.5)	0.575
LVEDD, cm	5.0±0.5	5.0±0.5	4.8±0.4	4.8±0.5	0.1 (−0.1 to 0.3)	0.347
LVESD, cm	3.1±0.4	3.3±0.4†	3.1±0.4	3.2±0.5	0.1 (−0.1 to 0.3)	0.466
Cardiac output, L/min	6.01±1.1	6.03±1.2	6.02±1.2	5.8±1.0	0.21 (−0.43 to 0.85)	0.507
Endothelial function						
FMD, % relative to baseline	9.9±5.2	8.1±3.9†	9.5±6.4	9.2±5.4	−1.5 (−4.0 to 0.9)	0.208
LnRHI	1.0±0.3	0.8±0.3†	0.8±0.3	0.7±0.2†	0.0 (−0.2 to 0.1)	0.629
Right-sided heart catheterization						
Cardiac output, L/min	6.9±1.6	7.0±1.7	6.6±1.7	6.9±1.5	−0.2 (−0.9 to 0.5)	0.611
MPAP, mm Hg	20.9±6.8	19.7±5.5	18.9±6.7	18.0±6.2	−0.3 (−3.0 to 2.4)	0.804
PCW, mm Hg	11.9±5.9	10.3±4.1	10.7±4.9	9.7±4.9	−0.6 (−3.1 to 2.0)	0.661
PVR, Wood units	1.4±0.7	1.3±0.9	1.4±0.7	1.2±0.6	0.1 (−0.2 to 0.4)	0.554
SVR, d·s·cm ^{−5}	1081±269	1195±341	1163±316	1189±429	88 (−93 to 269)	0.333
HRQOL						
VAS score (0–100 mm)		77±22		70±25	7 (−4 to 18)	0.196
PCS score	42±8	48±9*	43±8	49±8*	1 (−3 to 4)	0.762
MCS score	52±13	53±12	55±8	52±10	3 (−2 to 9)	0.170
HADS Anxiety score	3.7±3.4	3.9±3.3	3.5±3.1	4.2±4.2	−0.4 (−1.8 to 0.9)	0.525
HADS Depression score	3.1±3.4	2.9±3.2	2.2±2.3	2.1±2.3	−0.2 (−1.4 to 1.0)	0.741

a-v O₂ diff indicates arteriovenous oxygen difference; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration calculation); FEV₁, forced expiratory volume at 1 second; FMD, flow-mediated dilatation; HADS, Hospital Anxiety and Depression Scale; HIT, high-intensity interval training; HR, heart rate; HRQOL, health-related quality of life; hs, high-sensitivity; IQR, interquartile range; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LnRHI, log-transformed reactive hyperemia index; MCS, Mental Component Summary from Short Form-36, version 2; MICT, moderate-intensity continuous training; MPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCS, Physical Component Summary from Short Form-36, version 2; PCW, pulmonary capillary wedge pressure; PEF, peak expiratory flow; PVR, pulmonary vascular resistance; SBP, systolic blood pressure; SVR, systemic vascular resistance; and VAS, visual analog scale.

*P<0.001.

†P<0.05 within group.

‡P<0.05 between groups at baseline.

§Mann-Whitney U test.

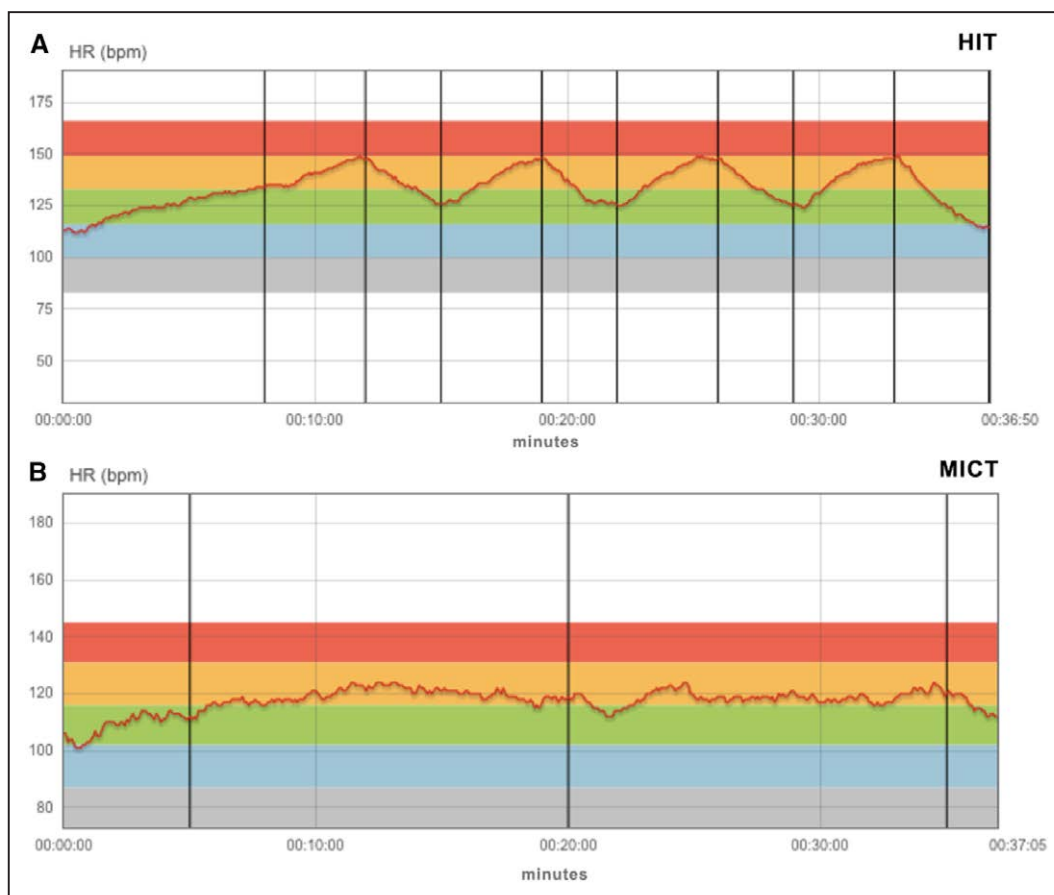


Figure 3. Illustration of the heart rate response (single patient) during a (A) high-intensity interval training (HIT) session and a (B) moderate-intensity continuous training (MICT) session, both close to the 1-year follow-up.

The different shades of gray illustrate the default settings of the heart rate (HR) monitors for different intensity zones.

the third and last period; the mean \pm SD length of the interval bouts increased from 2.3 \pm 0.7 minutes in the first period to 3.6 \pm 0.7 minutes in the last period (Table IV and Figure I in the online-only Data Supplement). Accordingly, the mean \pm SD peak HR increased from 124 \pm 14 to 142 \pm 17 bpm. In the MICT group, the mean exercise session length was similar throughout the intervention period (56 \pm 13 minutes), but this measurement also included all warm-up and stretching time. In this group, the average HR per session increased from a mean \pm SD of 111 \pm 15 bpm in the first exercise period to a mean of 121 \pm 16 bpm in the last period (Figure 3 and Table IV in the online-only Data Supplement). No serious exercise-related adverse event occurred in either group during the intervention period. The intervention could not be completed at 100% every week by all participants because some inactive periods occurred as a result of cytomegalovirus lung infections, other infections, 1 ankle fracture, 2 spinal compression fractures, 1 arrhythmia (atrial flutter), hospitalizations (elevated troponin T and proBNP [pro-B-type natriuretic peptide] [suspected rejections], nephrectomy, hernia), gastroenteritis, transplant rejections grades 1 and 2, 1 deep vein thrombosis, musculoskeletal problems (back, knee, trochanter bursitis,

and Achilles tendon), headache, family-related issues, insufficient time for exercise, symptoms of depression, and lack of motivation. Detailed reasons for not being able to complete all the 72 planned exercise sessions are presented in Table V in the online-only Data Supplement.

Cardiopulmonary Exercise Test

At the 1-year follow-up (Table 2), there was a significantly larger increase in V_{O_2} peak in the HIT group compared with the MICT group (Figure 4). The mean difference between groups in the V_{O_2} peak change was 1.8 mL \cdot kg $^{-1}\cdot$ min $^{-1}$ (95% CI, 0.05–3.5), or half of 1 metabolic equivalent. The result was verified in an ANCOVA analysis adjusted for the baseline values (Table III in the online-only Data Supplement). In addition, the HIT and MICT groups improved their V_{O_2} peak levels by 25% and 15%, respectively (Table 2 and Table VI in the online-only Data Supplement). The anaerobic threshold increased more in the HIT group than in the MICT group, with a significant mean change between groups of 0.28 L/min (95% CI, 0.08–0.46). The mean \pm SD respiratory exchange ratio was similar between groups at both baseline and the 1-year follow-up (1.19 \pm 0.09

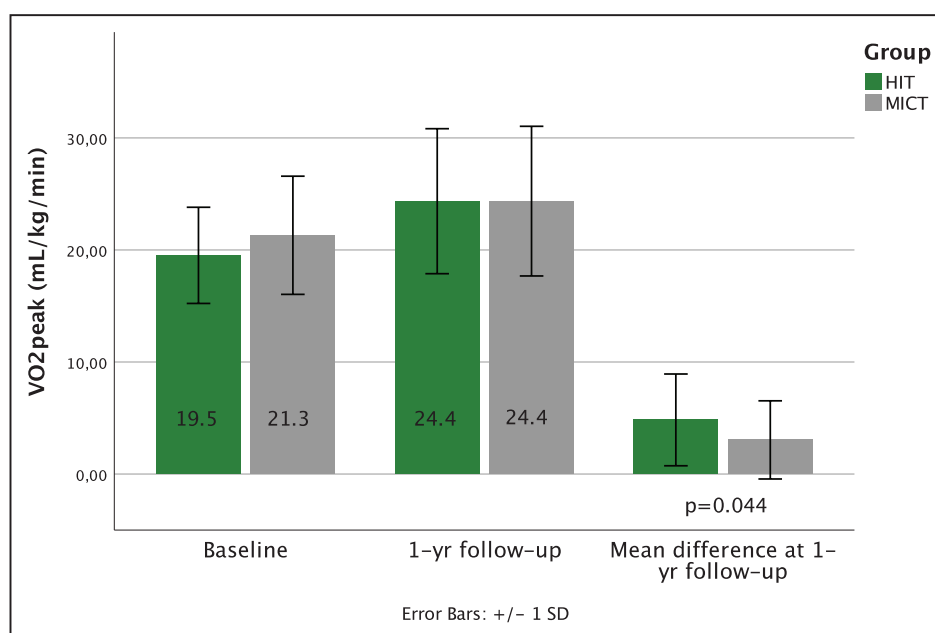


Figure 4. Peak oxygen consumption (Vo_2peak) at baseline and follow-up in the high-intensity interval training (HIT) group and the moderate-intensity continuous training (MICT) group and the mean change between groups at follow-up.

versus 1.22 ± 0.09 in the HIT and MICT groups, respectively); both groups had respiratory exchange ratios >1.10 , which indicated maximal levels of effort at both baseline and the 1-year follow-up. However, only the HIT group showed a significant improvement in the O_2 pulse (Table 2), which suggested an improved stroke volume.^{35,36} Chronotropic responses improved in both groups, but the peak HR was higher in the HIT group than in the MICT group at the 1-year follow-up (Table 2). Group-based correlations between the Vo_2peak and the O_2 pulse and peak HR are shown in Figure II in the online-only Data Supplement.

Subgroup analyses between subjects tested on the cycle ergometer versus the treadmill showed no differences in the mean change in Vo_2peak at follow-up in either the HIT or the MICT group (data not shown).

Determinants of the Change in Aerobic Capacity

Multiple linear regression analysis showed that the mean changes from baseline to the 1-year follow-up in HR reserve and O_2 pulse, including age and sex, accounted for 90% of the variance (adjusted R^2) in the mean change in Vo_2peak (liters per minute). All 4 variables contributed significantly to the model, in the following order of importance: O_2 pulse $>$ HR peak $>$ sex $>$ age (Table VII in the online-only Data Supplement). We also evaluated several other variables that were significant in univariate regression. In addition, we evaluated other clinically relevant predictors such as treatment arm, body mass index, muscular exercise capacity, biomarkers, endothelial function, spirometry, resting a-v O_2 diff,

measures from echocardiography, and right-sided catheterization, but these did not show statistical significance in the multiple regression analyses.

Secondary and Exploratory End Points

Both groups showed improvements in muscular strength and muscular exercise capacity. However, compared with the MICT group, the HIT group showed a significantly higher mean change in muscular exercise capacity at the 1-year follow-up; the difference in improvement between groups was 464 J (95% CI, 63–863; Figure 5). This difference was further underscored by the correlation between Vo_2 and muscular exercise capacity, which was stronger in the HIT group ($r=0.541$) than in the MICT group ($r=0.400$; Figure II in the online-only Data Supplement). Neither group showed changes in echocardiographic variables (eg, left ventricular dimension and ejection fraction) or the right-sided heart catheterization data obtained at rest (eg, pulmonary artery or wedge pressures, cardiac output, pulmonary vascular resistance, or systemic vascular resistance), except that the HIT group showed a significant increase in the left ventricular systolic dimension at the 1-year follow-up (Table 3). Indexes of myocardial stretch (NT-proBNP [N-terminal proBNP]) and ischemia/myocardial necrosis (high-sensitivity troponin T) decreased from baseline to follow-up in both groups, but the mean changes were not significantly different between groups. In addition, the changes in endothelial function were not different between groups (Table 3). The estimated a-v O_2 diff at rest increased significantly in the HIT group, but this change was not significantly different from the change

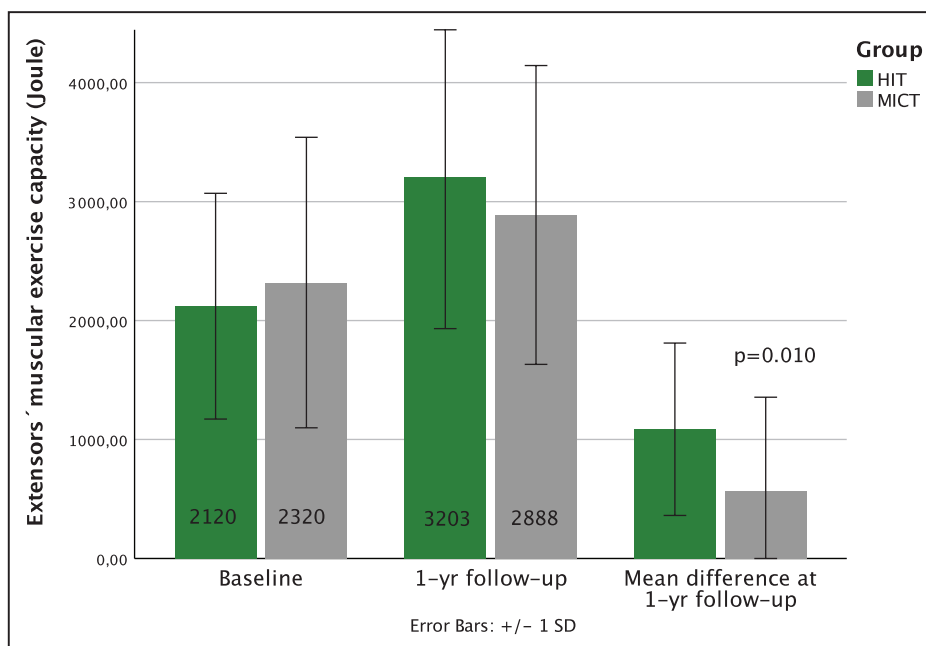


Figure 5. Muscular exercise capacity at baseline and follow-up in the high-intensity interval training (HIT) group and the moderate-intensity continuous training (MICT) group and the mean change between groups at follow-up.

observed in the MICT group at the 1-year follow-up (Table 2). Pulmonary function, assessed by peak expiratory flow, increased significantly more in the HIT group than in the MICT group (mean difference between groups, 11% [95% CI, 2–20]). The changes in FEV₁ were similar between groups (Table 3).

HRQOL, assessed with the Short Form-36, version 2, Hospital Anxiety and Depression Scale, and a visual analog scale, revealed no significant differences between the groups in terms of patient satisfaction and self-reported usefulness of the intervention (Table 3). At baseline, both groups had higher scores in the Short Form-36, version 2 Mental Component Summary than in the Physical Component Summary, but at the 1-year follow-up, both groups showed significant improvements in the Physical Component Summary ($P < 0.001$; Table 3). The HIT group had a numerically higher score on the visual analog scale at follow-up, but the difference between groups was not significant. Hospital Anxiety and Depression Scale scores were low in both groups at both time points (Table 3); this finding indicated a low degree of anxiety and depression symptoms during the course of the study. There was no significant difference in Hospital Anxiety and Depression Scale scores between the groups.

DISCUSSION

The most important finding in this study was that HIT was a safe, efficient method of exercise in de novo HTx recipients. We introduced this 9-month HIT intervention as early as 8 to 12 weeks after HTx. We found

that, compared with MICT, HIT resulted in clinically meaningful, significantly larger increases in the \dot{V}_{O_2} peak, anaerobic threshold, peak expiratory flow, and muscular exercise capacity (Tables 2 and 3). In addition, only the HIT group showed significant improvements in the resting a-v O_2 diff and O_2 pulse (within-group statistics).

As expected, exercise capacity increased significantly in both groups during the first year after HTx.^{18,25,37,38} Moreover, we found that the improvement in the \dot{V}_{O_2} peak was 1.8 mL·kg⁻¹·min⁻¹ greater with HIT compared with MICT. The magnitude of this \dot{V}_{O_2} peak increase was equal to or greater than those found in large studies in patients with heart failure who were treated with exercise alone (eg, the HF-ACTION study [Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training] showed an improvement at the 3-month follow-up of 0.6 mL·kg⁻¹·min⁻¹ in the exercise group versus 0.2 mL·kg⁻¹·min⁻¹ in the control group and at the 12-month follow-up of 0.7 mL·kg⁻¹·min⁻¹ in the exercise group versus 0.1 mL·kg⁻¹·min⁻¹ in the control group)³⁹ or patients treated with β -blockers,⁴⁰ angiotensin receptor blockers,⁴¹ or cardiac resynchronization therapy.⁴² The mechanism of this exercise effect remains unclear, but it is probably not related to exercise adherence or duration. High intensity appears to be a key factor in increasing the \dot{V}_{O_2} peak which suggests that HIT has unique effects on associated central factors, peripheral factors, or both.^{14,15,27,43}

The HIT intervention has not been conducted previously in de novo HTx recipients. Therefore, it was encouraging to find that none of the 3 patients who dropped out during the intervention reported any seri-

ous exercise-related adverse events. Our results underscore that a decentralized intervention model seems feasible. It also required fewer resources than many other intervention models.

Both groups had a mean Mental Component Summary score above the norm values, and none of the groups had mean scores that indicated any symptoms of anxiety or depression during the course of the study. Throughout the intervention period, the lower baseline Physical Component Summary scores improved significantly within both groups at the 1-year follow-up. Moreover, although patient satisfaction with the exercise program was not significantly different between groups, the HIT group scored higher on the visual analog scale at follow-up, indicating somewhat better patient satisfaction (Table 3). In addition, there were important differences between the HITS study and larger studies such as SMART-EX (*Study of Myocardial Recovery After Exercise Training in Heart Failure*) and HF-ACTION^{39,44} in terms of the organization, exercise protocol, and overall design. Typically, HTx exercise studies are relatively small, the population is relatively healthy, and the subjects are usually highly motivated to perform exercise training. In our study, the patients were actively involved in selecting where and with whom the exercise should be carried out. They also participated in planning the progression of the exercise. We are convinced that exercising in a 1:1 setting with a physical therapist was a key factor in achieving optimal adherence, exercise intensity, and health benefits. The exercise adherence was poorer and the increase in peak oxygen consumption in the intervention arm was smaller in the much larger HF-ACTION study than in our study. Smaller studies, particularly in a 1:1 setting, facilitate the management of monitoring and documenting the actual intensity achieved during exercise sessions, and this information is essential for true evaluations and firm conclusions on the effects of different exercise modes.

A recent review by Tucker et al⁶ addressed performance limitations in HTx recipients. They concluded that HTx recipients have reduced Vo_2peak through central and peripheral limitations and that exercise training increases Vo_2peak via peripheral adaptations. Consistent with that conclusion, in an earlier study on HTx recipients who were in maintenance status (1–8 years after HTx), we demonstrated that predictors of baseline Vo_2peak were mainly of peripheral origin.²⁶ Moreover, we found that the effects of a HIT intervention in that cohort were largely the result of peripheral adaptations.^{19,20} Similarly, a nonrandomized study conducted by Haykowsky et al¹⁸ in 18 de novo HTx recipients concluded that the exercise-induced increase in aerobic capacity was not associated with favorable improvements in left ventricular systolic function. However, measuring cardiac allograft function during exercise is highly challenging, and performing echocardiography

during submaximal exercise probably would not reveal the full impact of exercise on stroke volume.

In the current de novo cohort, the baseline Vo_2peak level was determined by both central (O_2 pulse and HR reserve) and peripheral (muscular exercise capacity) factors.²⁸ Many researchers have considered O_2 pulse, derived from cardiopulmonary exercise test, a surrogate for stroke volume.^{45–47} In the present study, we have taken O_2 pulse to represent a central factor. However, O_2 pulse also depends on peripheral oxygen extraction.

In the present study, we performed multiple regression analyses to compare our previously published baseline predictors,²⁸ with the follow-up values of the exact same predictors. The regression model sustained with O_2 pulse, HR reserve, age, muscular exercise capacity, body mass index, and sex (in order of importance), explaining 86% (adjusted R^2) of the variance in Vo_2peak .

However, when we evaluated factors that might explain the effect of exercise (the mean change in Vo_2peak at the 1-year follow-up) in a multiple regression analysis, we found that the effect was more dependent on alterations in central factors (HR peak and O_2 pulse) than on peripheral factors. Indeed, the change in muscular exercise capacity did not contribute significantly to the variance of the dependent variable (the mean change in Vo_2peak ; [Table VI in the online-only Data Supplement](#)). As described in the Results section, several other variables were also evaluated for their potential contribution to the change in Vo_2peak , but they did not reach statistical significance. These results might suggest that central factors, not surprisingly, dominate in the first phase after an HTx and that peripheral factors become more important after the first year. However, although in this cohort we could not see any significant exercise-mediated changes between groups in, for instance, the resting a-v O_2 diff or endothelial function, we could not rule out the possibility that those findings might have been evident in a larger, sufficiently powered cohort. The other central factors we tested (other than those mentioned above) were not significantly different between the groups at follow-up, including the change in chronotropic responses and measures derived from right-sided heart catheterization or echocardiography (Tables 2 and 3).

The present study showed significantly greater mean changes in muscular exercise capacity in the HIT group than in the MICT group. This difference implicates positive changes in skeletal muscle function and skeletal muscle oxidative metabolism and favorable peripheral vascular changes. These differences were further underscored by the strong correlation between the change in Vo_2peak and the change in muscular exercise capacity ([Figure II in the online-only Data Supplement](#)). These types of peripheral adaptations are consistent with findings in a recent study that demonstrated that HIT induced a rise in proangiogenic mediators that promot-

ed new vessel formation.⁴³ The significant difference in peak expiratory flow between groups at the 1-year follow-up might have contributed to the greater change in \dot{V}_{O_2} peak and the improved cardiorespiratory fitness⁴⁸ in the HIT group compared with the MICT group.

It is well known that exercise improves the \dot{V}_{O_2} peak, and exercise is a key aspect of rehabilitation after HTx. Recently, our research group also showed that improvements in the \dot{V}_{O_2} peak were related to better survival.⁸ However, the mechanisms underlying an improved \dot{V}_{O_2} peak and how they might be related to the differences between the HIT and MICT groups remain somewhat unclear. We require a better understanding of the central and peripheral contributions to the effects of exercise in HTx recipients and how these contributions might change with time after an HTx. With that understanding, we might be prepared to prescribe timed, individually tailored interventions to achieve optimal results with exercise.

Limitations

A central limitation of this study was the small sample size. Indeed, we did not attain the planned inclusion number according to the power analysis. A larger number would probably have strengthened the mean difference in \dot{V}_{O_2} peak values and the exploratory secondary end-point values at follow-up. Moreover, this limitation will likely affect results in the upcoming 3-year follow-up. Another limitation was that many of the evaluated variables were collected at rest (eg, the measures from echocardiography and right-sided heart catheterization and the a-v O_2 diff). Measurements at rest might not have reflected true changes that could have occurred during (peak) exercise. Furthermore, using O_2 pulse as a surrogate for stroke volume is a clear limitation and should be interpreted with caution. In addition, only supervised exercise was recorded in both groups. The performance of unsupervised exercise in both groups might have been useful information. Furthermore, a quadriceps muscle biopsy would have provided valuable insight into changes in different muscle fiber types, capillarization, muscle activity, and energy expenditure.

Conclusions

We found that HIT was a feasible, safe, and effective method of exercise in this cohort of de novo HTx recipients. Our findings suggest that implementing HIT could contribute to optimal general health outcomes and prognoses in this group of patients.

ARTICLE INFORMATION

Received July 6, 2018; accepted December 21, 2018.

The online-only Data Supplement is available with this article at <https://www.ahajournals.org/doi/suppl/10.1161/circulationaha.118.036747>.

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Acknowledgments

We thank all the patients and local physical therapists who dedicated nearly a year of their lives to participate in this study. We also thank Professor Eva Prescott for the international cooperation and for contributing to patient management. For assistance with the muscle strength testing among the Swedish participants, we thank PhD student Andreas Lundberg Zachrisson and Professor Stefan Grau from the University of Gothenburg. We also thank Kaspar Broch, MD, PhD, for valuable support and guidance throughout the study period.

Sources of Funding

This work was supported by grants from the Norwegian Health Association, the South-Eastern Norway Regional Authority, and Scandiatransplant.

Disclosures

None.

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CORRECTION

Correction to: Effect of High-Intensity Interval Training in De Novo Heart Transplant Recipients in Scandinavia: One-Year Follow-Up of the HITTS Randomized, Controlled Study

In the article by Nytrøen et al, "Effect of High-Intensity Interval Training in De Novo Heart Transplant Recipients in Scandinavia: One-Year Follow-Up of the HITTS Randomized, Controlled Study," which published online ahead of print on Feb 18, 2019, and in the May 7, 2019, issue of the journal (*Circulation*. 2019;139:2198-2211. doi: 10.1161/CIRCULATIONAHA.118.036747) a correction to the supplemental file is needed.

The online-only Data Supplement Table VII needed 2 corrections:

1. The negative coefficient (-0.77) for O₂ pulse was incorrect because the post-value was mistakenly subtracted from the pre-value. The standardized coefficient (beta) for O₂ pulse should be 0.77.
2. All the confidence intervals were incorrect, they corresponded to the unstandardized B and not the standardized beta values. Correct confidence intervals are now given.

The correction has been made to the online-only Data Supplement, which is available at <https://www.ahajournals.org/doi/abs/10.1161/CIRCULATIONAHA.118.036747>.

SUPPLEMENTAL MATERIAL

Supplemental tables

Supplemental table 1: A brief summary of the local immunosuppressive protocol:

1) Patients received induction therapy with IL-2 inhibitor Basiliximab at the time of surgery, and at day 4 after HTx. In Denmark and Sweden ATG induction therapy 1 or 2 mg/kg was administered for 3 days immediately after HTx.

2) Calcineurin inhibitors (CNI) were introduced 12 hours after HTx. In selected patients, CNI treatment was partially replaced with everolimus, and in some patients, CNIS were withdrawn and completely replaced with everolimus 7-11 weeks after HTx.

3) Other routine medication:

Mycophenolate was initiated at a dose of 2.0 g daily for female and 3.0 g daily for men. The doses were reduced in case of side effects, notably leucopenia. Steroid pulses were administered during and immediately after surgery. Per oral prednisolone was initiated at 0.2 mg/kg and tapered over weeks to a maintenance dose of 0.1 mg/kg. Steroid withdrawal under biopsy surveillance was occasionally performed in patients with side effects. All patients were treated with statins if tolerated.

Supplemental table 2: Detailed description of the intervention arms as per-protocol*

	HIT (high-intensity interval training)	MICT (moderate intensity continuous training)
Baseline testing (in-hospital)	8-12 weeks post HTx	8-12 weeks post HTx
Planned number (lower limit) of supervised exercise sessions to be performed locally throughout the intervention period (3-12 months post HTx)	72	72
Regular contact, via telephone and e-mail, between the hospital and the primary health care throughout the intervention period	Yes	Yes
Planned intensity	85-95% of peak effort (during the intervals)	60-80% of peak effort (continuous intensity)
Approximately planned duration of each session, including warm-up and stretching	40 min	40 min
Heart rate monitor	Yes	Yes
Period 1 (3-6 months post HTx) Weekly amount of exercise	1 HIT session, 1 resistance training session, (1 combined session)	2-3 exercise sessions (endurance and resistance training)
Face-to-face meeting in-hospital with main researcher / PhD student	6 months post HTx	6 months post HTx
Period 2 (6-9 months post HTx) Weekly amount of exercise	2 HIT sessions, (1 resistance training session)	2-3 exercise sessions (endurance and resistance training)
Period 3 (9-12 months post HTx) Weekly amount of exercise	3 HIT sessions	2-3 exercise sessions (endurance and resistance training)
Follow-up testing	12 months post HTx	12 months post HTx
<i>Actual performance</i>		
<i>Mean ±SD number of performed exercise sessions</i>	<i>58 ±22</i>	<i>58 ±22</i>
<i>Mean ±SD duration during exercise sessions</i>	<i>Increased from approx. 30 mins in period 1 to 45 mins period 3.</i>	<i>56 ±13 min (mean for all three periods which were quite similar)</i>
<i>Actual intensity kept during exercise in period 1 -3</i>	<i>See Supplementary table 4</i>	<i>See Supplementary table 4</i>

*Additional details about the exercise intervention is previously published in a design article in *Am Heart J.* 2016, 172, 96-105.

HTx, heart transplant; SD, standard deviation.

Supplemental table 3: Statistical calculation of the change in VO_{2peak} from baseline to 12 months follow-up using ANCOVA statistics.

	Actual mean (±SD) at follow-up	ANCOVA estimated marginal mean [95% CI] at follow-up	Actual mean change (±SD) at follow-up	ANCOVA Estimated marginal mean change [95% CI] at follow-up	Test of between-subjects effect p-value ANCOVA	Partial Eta Squared (effect size)
HIT group (n=37)	24.4 ± 6.5	25.4 [24.2, 26.6]	4.84 ± 4.10	4.95 [3.71, 6.19]	0.026	0.065
MICT group (n=40)	24.4 ± 6.7	23.4 [22.2, 24,6]	3.07 ± 3.46	2.97 [1.77, 4.16]		

SD, standard deviation; HIT, high-intensity interval training; MICT, moderate, intensity continuous training.

Supplemental table 4: The mean (\pm SD) maximal heart rate during interval bout 1-4 recorded in the first and last exercise period during a HIT and MICT session respectively.

HIT (n=36)	Period 1 (mean \pm SD)	Period 3 (mean \pm SD)
Average HR max (bpm) Interval bout 1	119 \pm 13	137 \pm 18
Average HR max (bpm) Interval bout 2	124 \pm 14	140 \pm 17
Average HR max (bpm) Interval bout 3	128 \pm 14	142 \pm 17
Average HR max (bpm) Interval bout 4	130 \pm 15	142 \pm 17
MICT (n=38)		
Average HR (entire session)	111 \pm 15	121 \pm 16
Average HRmax* during the session	124 \pm 17	140 \pm 20

HR, heart rate.

**This only reflects the highest HR registered during a session, and must be seen in relation to the average HR for the entire session.*

Supplemental table 5: Registered reasons for adverse events /not being able to complete the intervention 100% (i.e. perform 72 exercise sessions)

	Number of events in the HIT group	Number of events in the MICT group
Infections		
Lung infections*	2	2
Other infections*	5	7
Cytomegalovirus* (CMV)	4	1
Cardiac events		
Atrial flutter (hospitalization, cardioversion)	1	0
Suspected rejection (hospitalization)	1	0
Cellular rejections grade 1	3	2
Cellular rejections grade 2	0	1
Musculoskeletal problems		
Ankle fracture	1	0
Spinal compression fractures	1	1
Back pain	2	2
Knee pain	1	0
Achilles tendon pain	0	1
Trochanter bursitis	1	0
Upper body pain	1	2
Other medical issues		
Gastroenteritis (hospitalization)	2	0
Gastrointestinal*	0	3
Hernia repair (hospitalization)	1	2
Nephrectomy (hospitalization)	1	0
Deep vein thrombosis	1	0
Headache	1	0
Diabetes (hospitalization)	1	0
Dizziness	0	1
Psychosocial issues		
Family related issues	1	0
Symptoms of anxiety and depression	1	1
Lack of motivation	0	2
Other		
Not enough time to exercise	1	1
Total number of events	33	29

*With or without hospitalization

Supplemental table 6: Summary table of mean changes* in the main exercise-related variables

	HIT Mean [95% CI]	MICT Mean [95% CI]	t-test between groups p-value
VO _{2peak} (mL/kg/min)	4.83 [3.47, 6.20]	3.07 [1.96, 5.61]	0.044
% of predicted VO _{2peak}	13.2 [9.7, 16.8]	8.5 [5.6, 11.5]	0.040
Peak heart rate (bpm)	26 [20, 30]	20 [15, 25]	0.129
% of age-predicted maximum heart rate	15.4 [12.6, 18.1]	11.7 [8.7, 14.8]	0.078
Muscular exercise capacity extensors (Joule)	1016 [718, 1314]	551 [270, 833]	0.024

*The actual baseline and follow-up values for both groups are shown in Table 2 in the original paper.

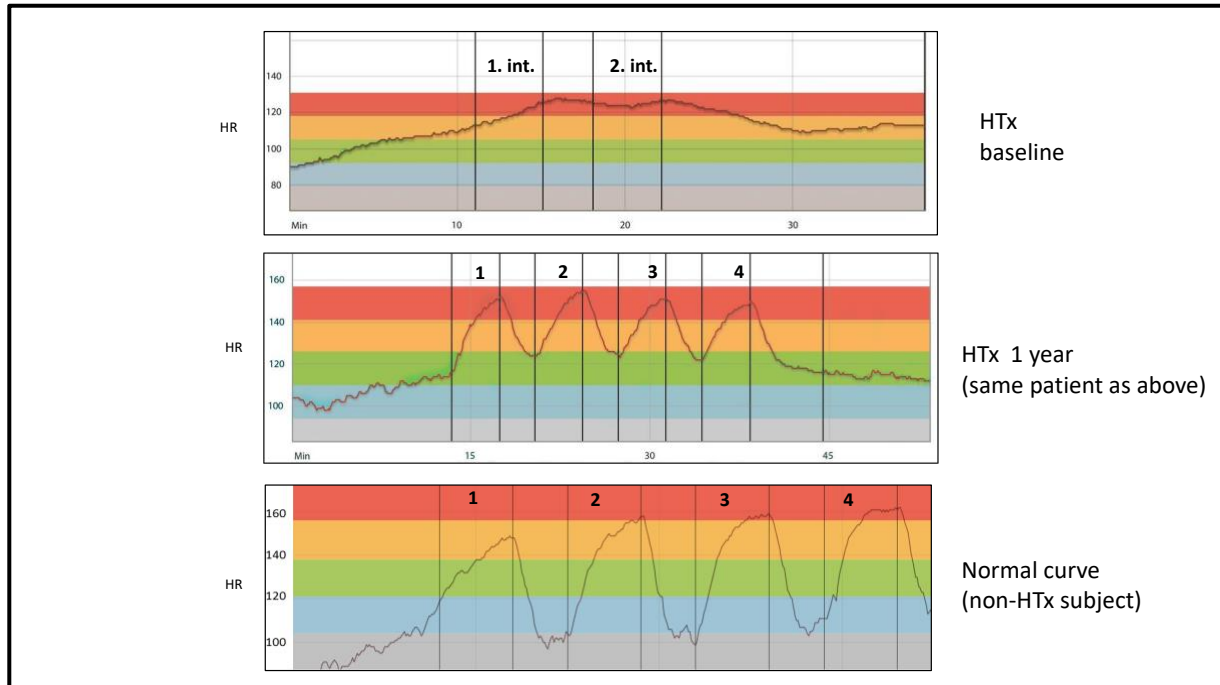
Supplemental table 7: Multiple regression analysis. Dependent variable mean change $\text{VO}_{2\text{peak}}$ L/min. Final model.

N = 70	Standardized coefficient Beta [95% CI]	P-value
Mean change O_2 -pulse (mL/beat)	0.77 [0.69, 0.85]	< 0.001
Mean change HR peak (beats/min)	0.53 [0.45, 0.61]	< 0.001
Sex	-0.16 [-0.24, -0.08]	< 0.001
Age (years)	-0.09 [-0.17, -0.01]	0.023
Adjusted R ²	0.90	

HR, heart rate.

Supplemental figures

Supplemental figure 1:



This figure enhances the heart rate (HR) in the HIT group shown in Supplementary table 4. It illustrates the HR improvement from baseline to follow-up (one single subject in the study), compared to a curve from a non-HTx subject at the bottom.

Supplemental figure 2:

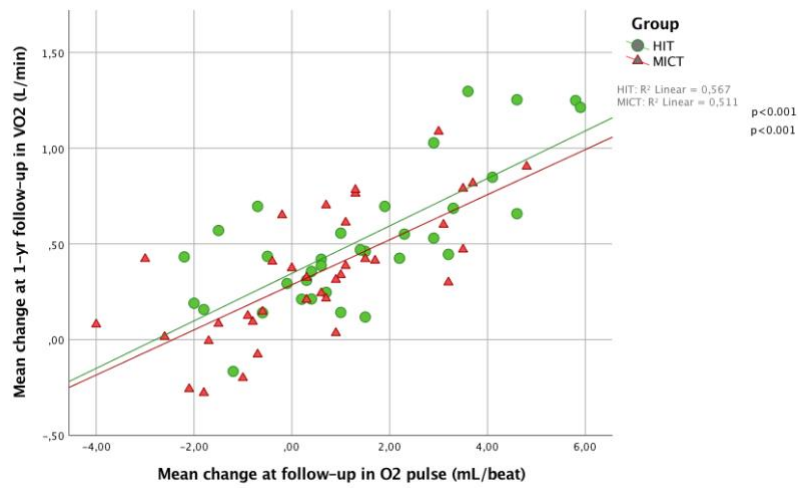


Figure A

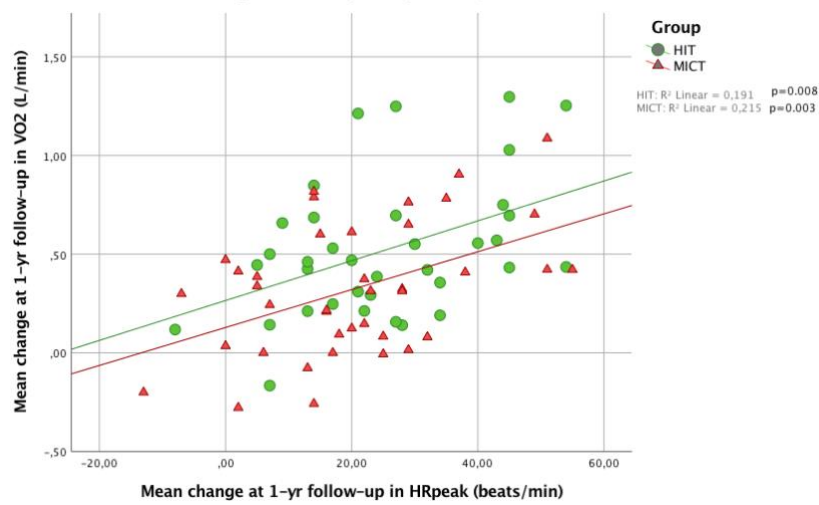


Figure B

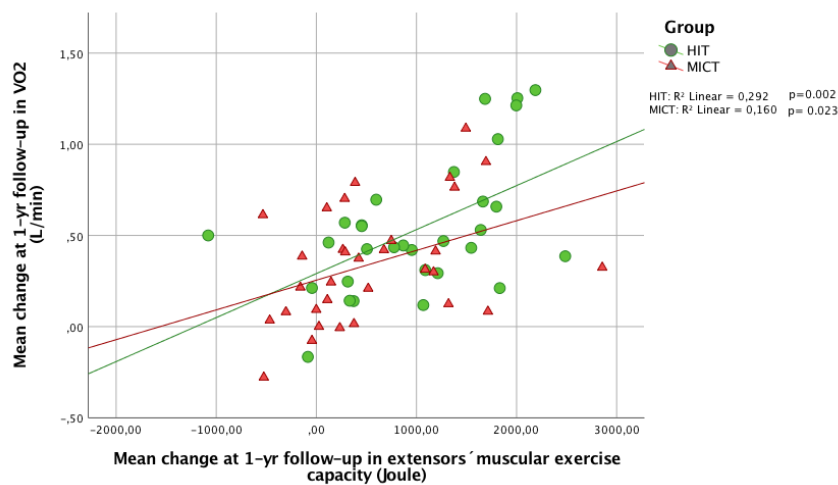


Figure C


Correlation between the mean change in VO_{2peak} , O_2 pulse (fig. A), change in peak heart rate (fig. B) and change in muscular exercise capacity (fig. C), according to group. The green circles represent the subjects in the HIT-group, and the red triangles represent the subjects in the MICT-group.

RESEARCH

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High-intensity interval training and health-related quality of life in de novo heart transplant recipients – results from a randomized controlled trial

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Abstract

Background: Studies on the effect of high-intensity interval training (HIT) compared with moderate intensity continuous training (MICT) on health-related quality of life (HRQoL) after heart transplantation (HTx) is scarce. No available studies among de novo HTx recipients exists. This study aimed to investigate the effect of HIT vs. MICT on HRQoL in de novo recipients.

Methods: The HITTS study randomized eighty-one de novo HTx recipients to receive either HIT or MICT (1:1). The HIT intervention were performed with 2–4 interval bouts with an intensity of 85–95% of maximal effort. The MICT group exercised at an intensity of 60–80% of their maximal effort with a duration of 25 min. HRQoL was assessed by the Short Form-36 version 2 (SF-36v2) and the Hospital Anxiety and Depression Scale, mean 11 weeks after surgery and after a nine months' intervention. The participants recorded their subjective effect of the interventions on their general health and well-being on a numeric visual analogue scale. Clinical examinations and physical tests were performed. Differences between groups were investigated with independent Student t-tests and with Mann-Whitney U tests where appropriate. Within-group differences were analyzed with Paired-Sample t-tests and Wilcoxon Signed Rank tests. Correlations between SF-36 scores and VO_{2peak} were examined with Pearson's correlations.

Results: Seventy-eight participants completed the intervention. Both exercise modes were associated with improved exercise capacity on the physical function scores of HRQoL. Mental health scores remained unchanged. No differences in the change in HRQoL between the groups occurred except for Role Emotional subscale with a larger increase in the HIT arm. Better self-reported physical function was associated with higher VO_{2peak} and muscle strength.

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Conclusion: HIT and MICT resulted in similar mean changes in HRQoL the first year after HTx. Both groups experienced significant improvements in the physical SF-36v2.

Trial registration: ClinicalTrials.gov number: [NCT01796379](https://clinicaltrials.gov/ct2/show/study/NCT01796379) Registered 18 February 2013.

Keywords: Health-related quality of life, Heart transplantation, High-intensity interval training, Moderate intensity continuous training, Oxygen consumption, Muscle strength, self-reported physical function, Exercise

Background

Heart transplantation (HTx) is the preferred therapy for selected patients with end-stage heart failure [1]. To improve physical capacity and health-related quality of life (HRQoL), cardiac rehabilitation is an integrated component in most HTx programs.

HRQoL is impaired prior to transplantation [2–4]. Longitudinal studies have reported that HRQoL improves significantly after HTx, with the greatest improvement occurring during the first half year [2, 5, 6]. Most of the studies assessing long-term HRQoL after HTx have shown that HRQoL remains good up to five, [2, 7] ten [8] and up to 20 [9] years after transplant.

The physical domains in HRQoL are lower in HTx recipients than in the general population [1, 10], while the mental health domains has been found comparable to the general population [7, 8]. The physical functioning subscale in the Short-Form-36 (SF-36v2) is related to peak oxygen consumption (VO_{2peak}), reflecting an association between self-reported physical function and objective measurements [11, 12]. The impact of exercise capacity on HRQoL has been studied at different time points after HTx [11–21]. Studies have found an association between improved exercise capacity and HRQoL [11, 19], but the effect of different exercise modes on HRQoL is unclear [1], mainly due to lack of high-quality studies. Only one small study has examined the effect of high-intensity interval training (HIT) vs. moderate intensity continuous training (MICT) on HRQoL in maintenance HTx recipients, but found no difference between the two groups [13]. The effect of HIT vs. MICT on HRQoL in newly heart transplanted recipients has not been studied, but these patients may have a greater potential for improvement in HRQoL [1].

The aim of this study was to investigate the effect of HIT vs. MICT the first year after heart transplantation. We hypothesized that HIT would improve HRQoL more than MICT in de novo HTx recipients.

Methods

The study-design and other results has been described earlier [22, 23]. In short, it was a multi-center, randomized controlled trial comparing HIT vs. MICT in adult, consenting de novo HTx recipients. The trial was conducted at three transplant-centers in Scandinavia. The

primary endpoint for the overall project was the change in VO_{2peak} , while the prespecified endpoint for this sub-study was the change in HRQoL. Eighty-one participants were included 7–16 weeks after HTx, and 78 were retested after nine months (Fig. 1). A permuted block randomization list was computer generated by a third party. Numbered sealed envelopes detailing the individual treatment allocation was prepared based on this list. Participants were assigned a randomization number at inclusion. After the CPET test at baseline, the envelope was opened and the patient was allocated to HIT or MICT.

Exercise intervention

The intervention is described elsewhere [22, 23]. Briefly, the participants were randomized 1:1, to either nine months of HIT or MICT at 11 ± 2 weeks after HTx. Participants in both groups exercised 2–3 times per week in the 9-month long intervention. The HIT consisted of 2–4 interval bouts at an intensity of 85–95% of maximal effort (corresponding to a rated perceived exertion (RPE) of 16–18). Between the HIT bouts, there was an active rest period (RPE 11–13). The goal for the HIT group was to be able to perform 4 interval bouts of 4 min length in the last intervention period. The MICT group followed the standard-of care exercise recommendations in recently HTx recipients, with an exercise intensity of 60–80% of maximal effort (corresponding to an RPE of 12–15) for a duration of 25 min. Both interventions included a 10 min warm up and a cool-down period of 5 min at the end of the exercise session. In addition, both groups performed strength training. All exercise sessions were performed in the participants' local communities, supervised by health personnel and all exercise sessions in both groups were logged and monitored with a heart rate monitor. Of 72 planned sessions, the HIT group completed median (interquartile range (IR)) 60 (28) sessions and the MICT group completed 56 (37) (p for difference 0.858).

Self-reported questionnaires

HRQoL was assessed by the generic questionnaire SF-36v2, [24] frequently used in HTx populations [1, 25]. The SF-36 is divided into eight subscales; Physical Functioning, Role Physical, Bodily Pain, General Health,

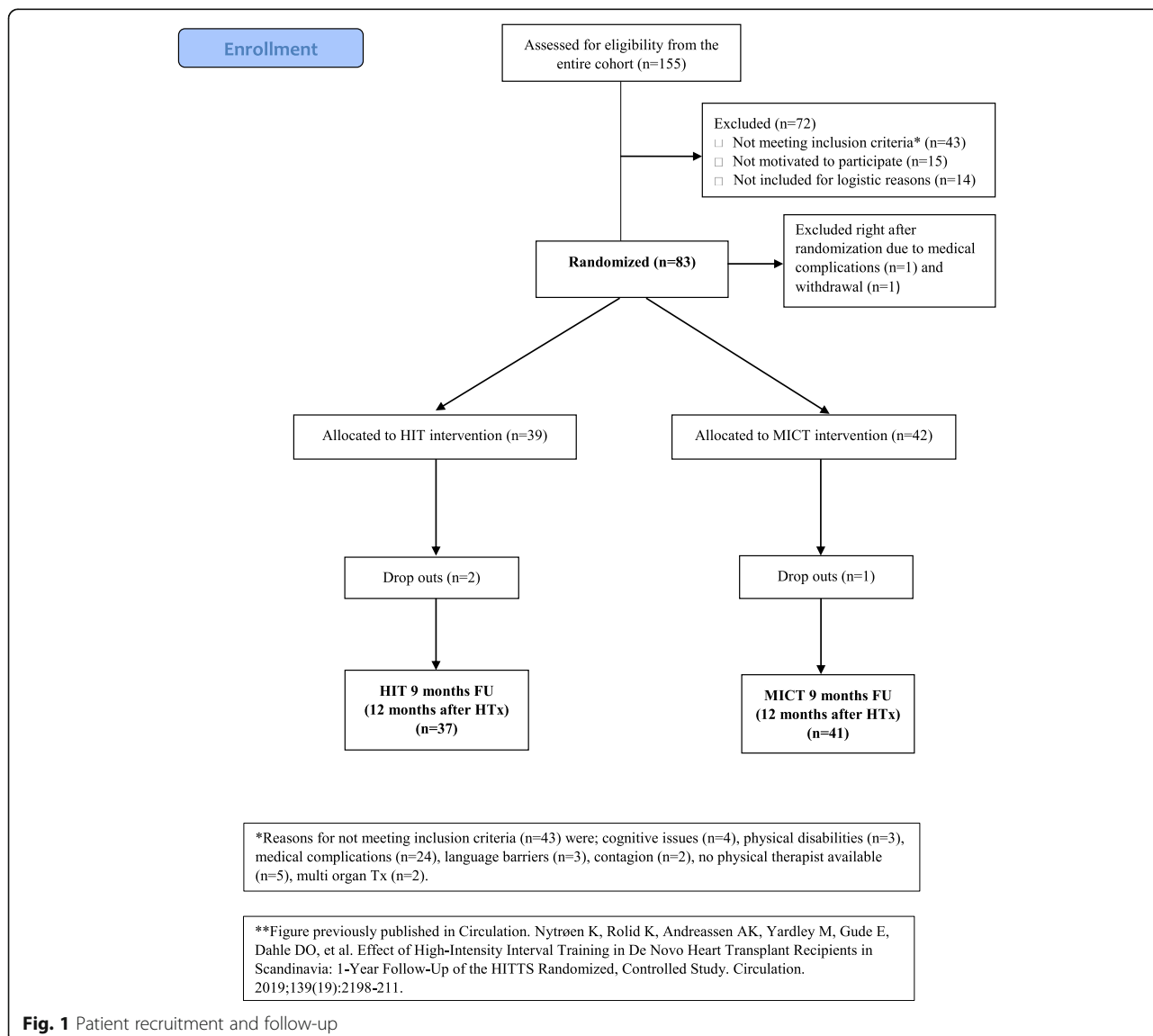


Fig. 1 Patient recruitment and follow-up

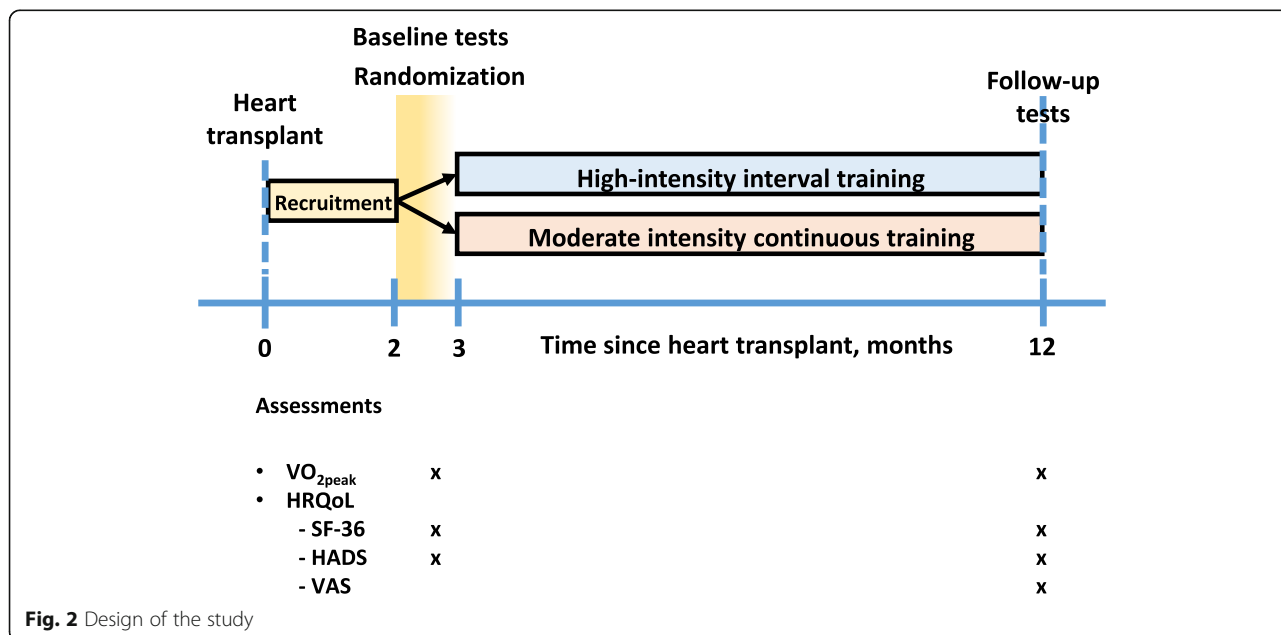
Vitality, Social Functioning, Role Emotional and Mental Health. The eight subscales aggregate into two summary scores; a Physical Component and a Mental Component; higher score indicating better HRQoL. In this study, all scores were transformed to norm-based values with a standardized mean of 50 and a standard deviation (SD) of 10. A change of 2–4 points on any item is considered to be of clinical significance [24].

Symptoms of anxiety and depression were measured with the Hospital Anxiety and Depression Scale (HADS) [26]. The participants’ socio-demographic background was assessed by a simple questionnaire at baseline and at follow-up. Additionally, at follow-up, all the participants recorded: “To what extent do you feel participation in this study had a positive impact on your general health and well-being” on a numeric visual analogue scale (VAS), ranging from “not at all” to “to a very great extent”.

All the questionnaires were self-administered and filled out during the study visits at both time points (Fig. 2). The Physical Functioning subscale from SF-36v2 was selected to represent self-reported physical function.

Exercise testing

All participants underwent a cardiopulmonary exercise test (CPET) with measurements of VO_{2peak} at baseline and at follow-up. Most of the Norwegian participants (n = 70) in were tested on a treadmill with breath-by-breath gas analysis (Jaeger® Masterscreen® CPX, Carefusion), and four of the participants were tested on a bicycle (Schiller Cardiovit® CS-200 Excellence). The participants from Sweden and Denmark (n = 7) were tested on a bicycle (Jaeger®, Oxy Con Pro® and Jaeger® Vyntus® CPX). The CPET tests was performed with an individualized protocol with a gradual increase in



workload until exhaustion [22, 27]. Isokinetic muscle strength and muscular exercise capacity in the lower limbs were measured with a dynamometer (Cybex 6000) [22, 23, 28].

Ethics

All participants provided written informed consent prior to inclusion. The study was approved by the regional ethic committees in Norway, Sweden and Denmark. The study is conducted according to the Helsinki Declaration. <https://clinicaltrials.gov/> identifier NCT01796379.

Statistics

Continuous data are expressed as mean ± SD, or median (IR). Categorical data are presented as number and percentages. An intention-to-treat analysis were conducted. Differences between the two groups were investigated with independent Student t -tests and with Mann-Whitney U tests where appropriate. The change (delta value) for each participant between baseline and 1-year follow-up was calculated by subtracting the results at 1-year follow-up with the results at baseline [Change = 1-year follow-up – baseline]. The change was assessed by independent t-tests to calculate the mean difference in change between the two groups in normally distributed variables, and by Mann-Whitney U tests for variables with skewed distribution. Within-group differences were analyzed with Paired-Sample t-tests and Wilcoxon Signed Rank tests. We assessed associations between HRQoL scores and parameters reflecting exercise capacity using Pearson’s and Spearman’s correlations. Missing data in the SF-36v2 were handled by the “half-scale” rule, which means that a scale score was calculated if at

least half of the items of that specific scale were answered [24]. For the two HADS scales, scores were calculated for those with complete data only. All data were analyzed using IBM SPSS 25.0 (IBM Corporation, United States). P values < 0.05 (two-sided) were considered statistically significant.

Results

Demographic data are provided in Table 1. There were no differences between the intervention arms regarding baseline socio-demographic or clinical characteristics.

All HRQoL variables were similar in the two groups at baseline. Symptoms of depression and anxiety were low in both groups at baseline (Table 2).

During the intervention, the scores for the SF-36v2 subscales Physical Functioning and Role Physical improved significantly in both exercise arms (Table 2). The improvement in these scales exceeded two points, which is regarded a clinically important difference [24]. Accordingly, the Physical Component Summary scores improved significantly (Table 2). The Mental Component Summary scores were above 50 at baseline, while HADS scores were low. Neither the Mental Component Summary scores nor the HADS scores did change significantly during the intervention period (Table 2).

The participants’ general health and well-being was good, as shown on the VAS scale. At follow-up, the HIT group scored 82 points and the MICT group scored 76 (p for difference = 0.235) (Table 2).

As reported earlier, there was a significant between-group difference in increased VO_{2peak} over the intervention period, in favor of HIT [23] (Table 3). However, there were no differences between the two exercise arms

Table 1 Baseline characteristics in the HIT group and the MICT group^a

Variables	HIT (n = 37)	MICT (n = 41)
Sex n (%) men	28 (76)	29 (71)
Age (years)	50 ± 12	48 ± 14
Body Mass Index kg/m ²	24.8 ± 3.4	25.6 ± 3.9
In a relationship (married/cohabitant)	22 (61)	30 (73)
Employed	8 (22)	9 (22)
Primary diagnosis n (%)		
CM/CAD/Other	21 (57) / 14 (38) / 2 (5)	31 (75) / 6 (15) / 4 (10)
Donor age (years)	37 ± 14	39 ± 14
Ischaemic time (min)	181 ± 77	184 ± 82
Median (IR) years of HF duration pre HTx	4.0 (9.1)	4.5 (8.1)
Median (IR) days on waitlist	85 (192)	71 (167)
Smoking (n (%) No/Ex-smoker)	18 (49) / 19 (51)	21 (51) / 20 (49)
Biomarkers		
Hemoglobin (g/dL)	11.8 ± 1.8	11.7 ± 1.6
Creatinine (µmol/L)	116.1 ± 33.9	118.5 ± 28.0
eGFR (mL/min/1.73m ²)	65.1 ± 20.9	62.7 ± 23.3
HbA1c (%)	5.7 ± 0.9	5.6 ± 0.7
Medication at inclusion n (%)		
Ciclosporine	24 (65)	31 (76)
Tacrolimus	11 (30)	10 (24)
Everolimus	12 (32)	13 (32)
Prednisolone	37 (100)	41 (100)
Mycophenolate	34 (92)	36 (88)
Statin	36 (97)	41 (100)
Beta blocker	9 (24)	12 (30)
Calcium blocker	8 (22)	12 (30)
ACE inhibitor	0	2 (5)
ARB	4 (11)	3 (8)
Diuretics	31 (84)	32 (78)

Variables are presented as mean ± standard deviation, median (interquartile range (IR)) or number (percentages). ACE angiotensin converting enzyme, ARB angiotensin II receptor blocker, CAD coronary artery disease, CM cardiomyopathy, eGFR estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration calculation), HbA1c hemoglobin A1c, HF heart failure, HIT High-intensity interval training, HTx heart transplantation, MICT moderate intensity continuous training

^aNo difference between groups

in HRQoL, the main endpoint of this substudy, except on the Role Emotional subscale, which covers the spectrum of mental health-related role constraints related to work or other daily activities [24] (Table 3). Maximal RPE (Borg's scale score) were equal between the two groups and did not change during the intervention period [23] (Table 3).

There were no differences between groups regarding rejections or serious/adverse events during the intervention period [23].

There was a positive correlation between VO_{2peak} and the self-reported physical function in both groups, both at baseline (Fig. 3) and at follow-up (Fig. 4). In the HIT

group, we found a modest correlation between the change from baseline to 1-year follow-up in self-reported physical function and the change in VO_{2peak} (Pearson's $r = 0.35$, $p = 0.03$). There was no correlation between the corresponding changes in the MICT group (Pearson's $r = -0.13$, $p = 0.41$).

The self-reported physical function also correlated with the extensors' maximal muscle strength and muscle endurance at both time points in both groups (See Additional File 1, Figs. 1, 2, 3 and 4).

The SF-36 Role Physical scale correlated modestly with VO_{2peak} in both groups at 1-year follow-up. Correlations between other CPET values (heart rate variables,

Table 2 Baseline and follow-up results in the HIT group and the MICT group^d

Variables	Baseline	Follow-up HIT (n = 37)	t-test, P value	Baseline	Follow-up MICT (n = 41)	t-test, P value
Health-related quality of life SF-36v2 components summaries and subscales						
Physical Component Summary (PCS)	42.2 ± 7.6	48.4 ± 9.3	< 0.001	43.2 ± 7.7	49.0 ± 8.4	< 0.001
Mental Component Summary (MCS)	52.5 ± 12.9	53.4 ± 11.9	0.673	55.1 ± 8.2	52.5 ± 9.6	0.086
Physical Functioning	45.0 ± 7.0	50.8 ± 6.0	< 0.001	46.4 ± 6.4	51.6 ± 6.6	< 0.001
Role Physical	37.6 ± 10.4	48.1 ± 9.3	< 0.001	40.8 ± 10.0	47.0 ± 10.0	< 0.001
Bodily Pain	47.8 ± 9.3	50.5 ± 10.5	0.163	48.1 ± 9.2	49.1 ± 12.2	0.583
General Health	48.2 ± 9.4	50.8 ± 11.0	0.067	49.8 ± 7.3	51.2 ± 9.4	0.292
Vitality	50.6 ± 10.8	52.6 ± 12.7	0.196	51.2 ± 9.4	53.6 ± 9.0	0.031
Social Functioning	46.7 ± 9.9	50.2 ± 9.1	0.047	48.7 ± 8.7	50.7 ± 9.0	0.278
Role Emotional	46.8 ± 13.1	52.0 ± 9.1	0.027	50.7 ± 7.7	48.7 ± 10.5	0.246
Mental Health	53.1 ± 11.0	53.7 ± 9.7	0.684	55.4 ± 7.8	54.0 ± 9.7	0.232
HADS Anxiety median (IR)	3.0 (3.5)	2.0 (4.5)	0.310 ^a	3.0 (3.5)	3.0 (4)	0.400 ^a
HADS Depression median (IR)	2.0 (3.5)	2.0 (4.8)	0.331 ^a	1.0 (2.5)	1.0 (3.8)	0.866 ^a
VAS scale (0–100) median (IR) ^b		82.0 (20.5)			75.5 (37.3)	0.235 ^c
Cardiopulmonary exercise test						
VO _{2peak} (mL/kg/min)	19.5 ± 4.3	24.4 ± 6.5	< 0.001	21.3 ± 5.3	24.4 ± 6.7	< 0.001
% of predicted VO _{2peak}	53.3 ± 11.6	66.6 ± 15.4	< 0.001	58.4 ± 12.5	66.9 ± 14.8	< 0.001
RPE (Borg scale score)	18.7 ± 0.5	18.8 ± 0.6	0.290	18.5 ± 1.1	18.8 ± 0.7	0.098
RER	1.17 ± 0.11	1.19 ± 0.1	0.314	1.22 ± 0.13	1.22 ± 0.1	0.751
Muscular capacity						
Maximal muscle strength extensors (Newton meter)	184 ± 74	237 ± 81	< 0.001	186 ± 73	222 ± 80	< 0.001
Muscular exercise capacity extensors (Joule)	2154 ± 952	3170 ± 1267	< 0.001	2319 ± 1201	2870 ± 1240	< 0.001

Health-related quality of life, exercise capacity and muscular strength at baseline (~ 11 weeks after HTx and at 9 months intervention (first yearly annual follow-up). Variables are presented as mean ± standard deviation or median (Interquartile range (IR)). HADS Hospital Anxiety and Depression Scale, HIT High-intensity interval training, MICT moderate intensity continuous training, RER Respiratory exchange ratio, RPE Rated perceived exertion, VAS visual analogue scale

^aWilcoxon Signed Rank Test

^bMeasured at follow-up only

^cMann-Whitney U test (difference between groups at follow-up)

^dNo difference between groups at baseline

O₂ pulse, maximal ventilation, respiratory exchange ratio, RPE) and SF-36 subscales were weak in both groups at both time points. However, there was a moderate correlation between metabolic equivalents and self-reported physical function in both groups at both time points (data not shown).

Missing data in the questionnaires

There was little missing data. At baseline there were 1.3% missing for the following SF-36 subscales; Role Physical, Vitality and Mental Health and 2.6% missing for the Role Emotional subscale and each of the two SF-36 sum scores. At follow-up there were 1.3% missing for all of the SF-36 subscales except of General Health and Social Functioning, while there were 2.6% missing for each of the two SF-36 sum scores and for each of the HADS scores.

Discussion

The main findings in the present study were: 1) In patients who had recently undergone HTx, the Physical Component Scores improved significantly during the nine-months long intervention period, and 2) There were no differences in HRQoL between patients allocated to HIT or MICT, except on the Role Emotional subscale where the HIT group had a significantly higher score.

Maintenance HTx recipients tend to score lower than the general population on the physical function domains of HRQoL [7, 8]. Interventions to improve physical function in HTx recipients are of special interest since improved physical function is associated with better HRQoL [11, 17] and is a strong predictor for survival [12].

In exercise trials comparing HIT with a control group in maintenance HTx recipients, improvements in

Table 3 Comparison of change between the HIT group and the MICT group from baseline to follow-up

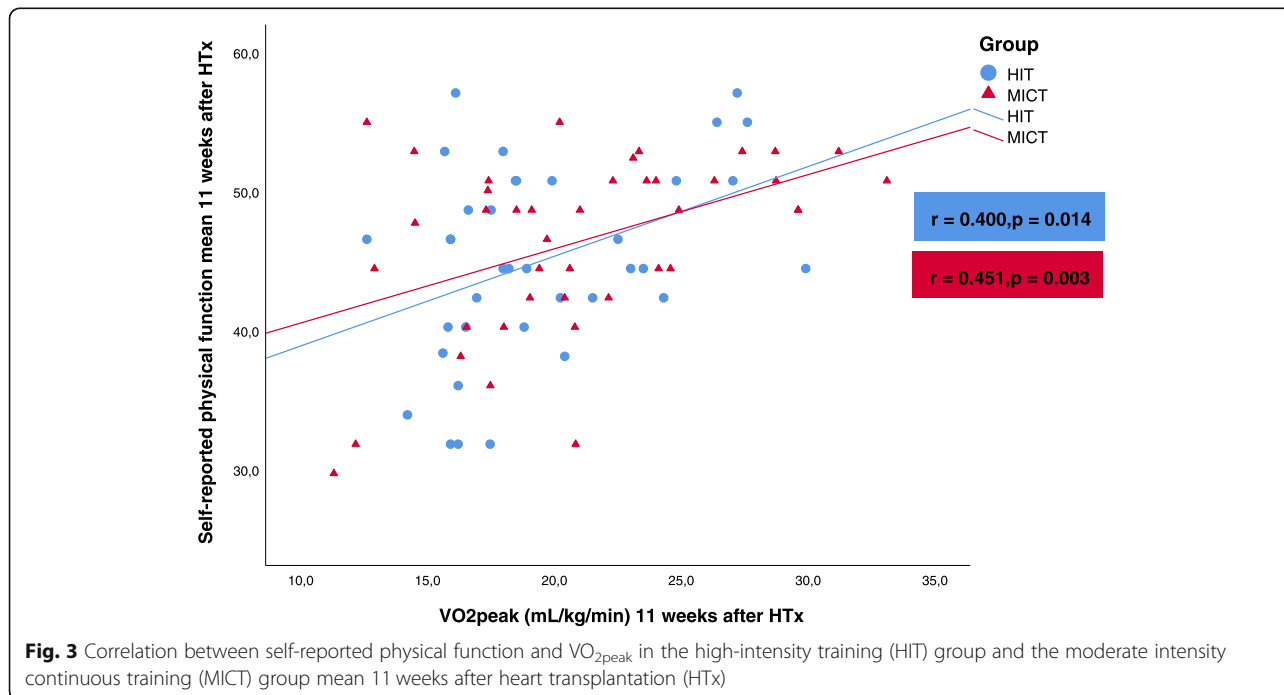
Variables	Change within the HIT group Mean ± SD (n = 37)	Change within the MICT group Mean ± SD (n = 41)	Difference in mean change between groups mean [95% CI]	P value Difference in change between groups
Health-related quality of life SF-36v2 components summaries and subscales				
Physical Component Summary (PCS)	6.3 ± 8.2**	5.7 ± 5.7**	0.6 [- 3.1, 4.2]	0.762
Mental Component Summary (MCS)	0.9 ± 12.5	- 2.6 ± 9.3	3.4 [- 1.5, 8.5]	0.170
Physical Functioning	5.8 ± 5.6**	5.2 ± 5.6**	0.6 [- 2.0, 3.2]	0.653
Role Physical	10.5 ± 11.2**	6.2 ± 10.0**	4.3 [- 0.6, 9.1]	0.082
Bodily Pain	2.7 ± 11.5	1.0 ± 11.4	1.7 [- 3.5, 6.9]	0.509
General Health	2.6 ± 8.3	1.4 ± 8.6	1.1 [- 2.7, 4.9]	0.555
Vitality	2.0 ± 9.2	2.6 ± 7.3*	- 0.6 [- 4.3, 3.2]	0.760
Social Functioning	3.6 ± 10.5*	2.0 ± 11.6	1.5 [- 3.5, 6.5]	0.541
Role Emotional	5.2 ± 13.4*	- 2.0 ± 11	7.2 [1.6, 12.8]	0.012
Mental Health	0.6 ± 9.0	- 1.4 ± 7.3	2.0 [- 1.7, 5.7]	0.284
HADS Anxiety	- 1.0 ^a	- 0.8 ^a		0.920 ^c
HADS Depression	- 1.0 ^b	- 0.2 ^a		0.427 ^c
Cardiopulmonary exercise test				
VO _{2peak} (mL/kg/min)	4.8 ± 4.1**	3.1 ± 3.5**	1.8 [0.1, 3.5]	0.044
Improvement in mL/kg/min (%)	25.2 ± 21.1**	15.1 ± 17.8**	10.1 [1.3, 19.0]	0.025
% of predicted VO _{2peak}	13.2 ± 10.7**	8.5 ± 9.1**	4.7 [0.2, 9.2]	0.040
RPE (Borg scale score)	0.1 ± 0.8	0.3 ± 1.2	0.2 [- 0.3, 0.7]	0.424
RER	0.02 ± 0.1	- 0.01 ± 0.1	0.02 [- 0.03, 0.1]	0.338
Muscular capacity				
Maximal muscle strength extensors (Newton meter)	54 ± 49**	36 ± 34**	178 [- 3, 39]	0.094
Muscular exercise capacity extensors (Joule)	1016 ± 812**	551 ± 780**	464 [63, 863]	0.024

Health-related quality of life, exercise capacity and muscular strength at baseline (~ 11 weeks after HTx and at 9 months intervention (first yearly annual follow-up). Variables are presented as mean ± standard deviation. CI Confidence Interval, HADS Hospital Anxiety and Depression Scale, HIT High-intensity interval training, MICT moderate intensity continuous training, SD standard deviation, RER Respiratory exchange ratio, RPE Rated perceived exertion, VAS visual analogue scale
 Within group: **p < 0.001, *p < 0.05
^aBased on negative ranks
^bBased on positive ranks
^cMann-Whitney U test

general health is higher in the intervention groups [14, 15]. These results suggest that exercise has a positive effect on HRQoL in the long term after HTx. In line with our findings, Hsu et al. [16] observed improved HRQoL in the physical function domains of SF-36 after cardiac rehabilitation early after HTx. It should be noticed that neither our study, nor the study by Hsu et al., [16] had a control group without an exercise program. The relatively high HRQoL observed at the end of our trial, and in the study by Hsu et al. [16] may reflect an overall improved health status during the first year after HTx, rather than an effect of exercise alone. For example, Ortega et al. [29] found improvements in SF-36 physical domains over the first year after HTx without an intervention.

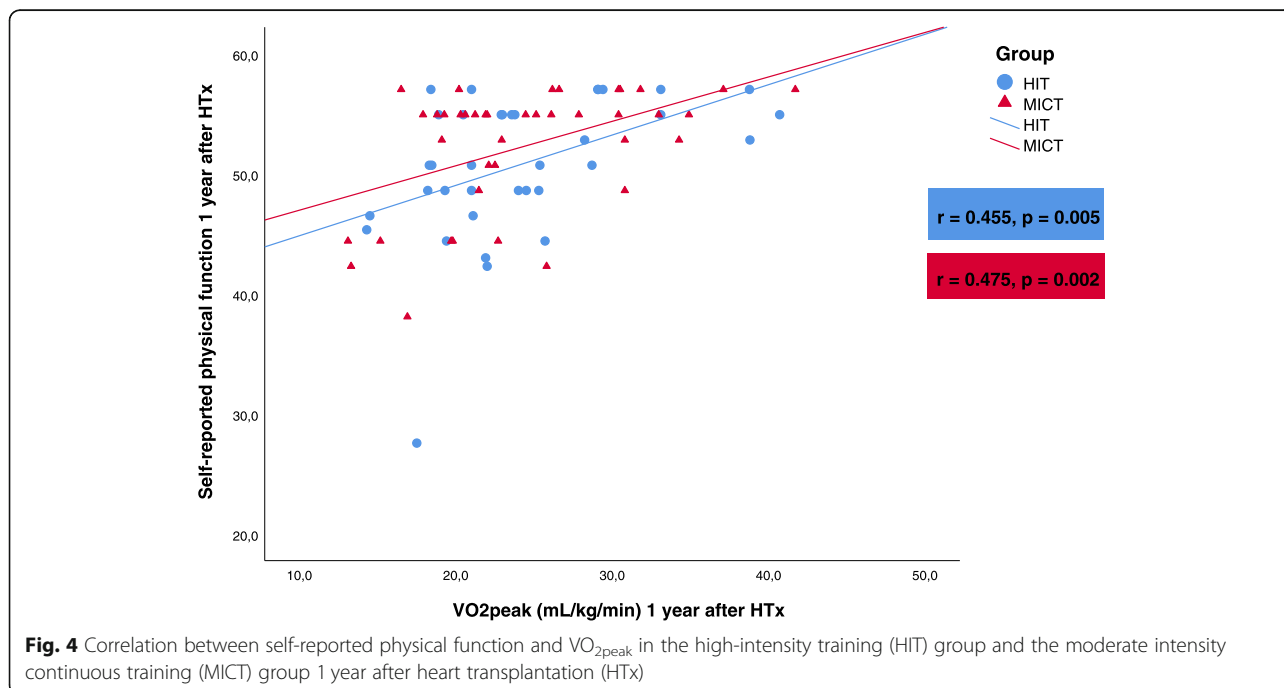
To our knowledge, only one prior study has investigated the effect of HIT vs. MICT on HRQoL in HTx recipients [13]. In this crossover trial (n = 16), [13] there were no differences between the groups regarding HRQoL, symptoms of anxiety or depression, which is in line with our results. However, the same study found a significant decrease in symptoms of anxiety in the HIT group, and a significant decrease in symptoms of depression in both groups. This contrasts our study, where symptoms of depression and anxiety were low and stable throughout the intervention period in both groups.

The improvement in the Role Emotional subscale in our patients randomized to HIT may reflect an improved sense of achievement associated with exhaustive exercise, but may also be an incidental finding.



We found correlations between VO_{2peak} and self-reported physical function at both time points, as previously reported in maintenance HTx recipients [19]. The correlation between the change in self-reported physical function and the change in VO_{2peak} from baseline to 1-year follow-up was observed in the HIT group only. This may be due to the higher mean change in VO_{2peak} in the HIT group compared to the MICT group. VO_{2peak} and

self-reported physical function are strong predictors for long-term survival after HTx [12]. Obtaining self-reported physical function is less resource-demanding than performing CPET with measurements of VO_{2peak} . However, the correlation between the two is modest, and self-reported physical function cannot fully substitute VO_2 measurements in the short and in the longer term after HTx.



Limitations

The high baseline HRQoL scores may reflect an above average healthy population and may also have affected the impact of the intervention on HRQoL. For obvious reasons, the sickest patients could not be enrolled in the trial. Thus, our results may not be valid for the entire HTx population. HRQoL was a secondary, but prespecified endpoint in the HITTs (High-intensity Interval Training in De Novo Heart Transplant Recipients in Scandinavia) study [22, 23]. With only 78 participants we may face a type II error due to insufficient statistical power.

A disease-specific HRQoL questionnaire could have been more sensitive to detect differences between groups. So far, no disease-specific questionnaires in Norwegian are available for the HTx population. In a prior HTx study, we experienced a ceiling effect using the heart failure-specific Kansas City Cardiomyopathy Questionnaire [30] and decided not to use this questionnaire in this study.

The HITTs trial [22, 23] was not designed to assess the participants' daily activities and the roles they were hoping to assume. This limits our ability to explain the between-group difference in the Role Emotional scale.

Clinical implications and future directions

Interventions for good and stable HRQoL, both short- and long-term after HTx, are needed. Exercise yields better physical function and makes it easier to engage in various activities of everyday life. However, despite improved VO_{2peak} with the HIT intervention, HRQoL was similar in both intervention arms. The development of an organ transplant-specific HRQoL questionnaire is warranted for future research in this field, [25] as it probably will be more accurate to detect changes in health status associated with organ transplant issues.

Conclusion

This randomized controlled trial demonstrated significant improvements in the physical function components in HRQoL over a nine-month long exercise intervention in de novo HTx recipients. However, despite a larger improvement in exercise capacity in the HIT group, there were no between-group differences regarding the change in HRQoL.

Supplementary information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s12955-020-01536-4>.

Additional file 1: Figure 1. Correlation between self-reported physical function and maximal muscle strength in the high-intensity training group and the moderate intensity continuous training group 11 weeks after heart transplantation (HTx). **Figure 2.** Correlation between self-reported physical function and maximal muscle strength in the high-

intensity training group and the moderate intensity continuous training group 1 year after heart transplantation (HTx). **Figure 3.** Correlation between self-reported physical function and muscle endurance in the high-intensity training group and the moderate intensity continuous training group 11 weeks after heart transplantation (HTx). **Figure 4.** Correlation between self-reported physical function and muscle endurance in the high-intensity training group and the moderate intensity continuous training group 1 year after heart transplantation (HTx).

Abbreviations

CPET: Cardiopulmonary exercise test; HADS: Hospital Anxiety and Depression Scale; HIT: High-intensity interval training; HITTs: High-intensity Interval Training in De Novo Heart Transplant Recipients in Scandinavia; HRQoL: Health-related quality of life; HTx: Heart transplantation/Heart transplant; IR: Interquartile range; MICT: Moderate intensity continuous training; RPE: Rated perceived exertion; SD: Standard deviation; SF-36v2: Short Form-36 version 2; VAS: Visual analogue scale; VO_{2peak} : Peak oxygen consumption

Acknowledgements

We want to thank all the HTx recipients for participating in the HITTs study. Thanks to professor Finn Gustafsson at Rigshospitalet, Copenhagen and professor Eva Irene Bossano Prescott, Bispebjerg Frederiksberg Hospital for help with planning the study. We also thank physical therapist Julia Philip Wigh at Sahlgrenska University Hospital for help with the coordination of the Swedish population and Professor Stefan Grau and PhD student Andreas Lundberg Zachrisson for help with the muscle strength testing of the Swedish population.

Published abstract

Part of this work is earlier presented at the International Society for Heart and Lung Transplantation 38th and 39th Annual Meeting and Scientific Sessions in April 2018 [31] and in April 2019 [32, 33].

Authors' contributions

KR coordinated the study, collected data, analyzed and drafted the paper. AKA, EG and KB were principal investigator responsible for the participants in Norway and were involved in the inclusion of the participants. MY and EB collected data and contributed to coordination of the study. ARA and IG were engaged in both the inclusion process of the participants and the coordination in-hospital in Norway. CHD coordinated the exercise intervention and collected data in Denmark. KIP contributed especially to the HRQoL part of the study. KK was responsible for the study in Sweden. LG and KN were the principal investigators, designed the study, drafted and revised the paper. All authors have contributed in revisions and to the final version of this paper.

Funding

This work was supported with a PhD grant from the Norwegian Health Association (grant number 12906), a post-doctoral grant from the South-Eastern Norway Regional Health Authority (grant number 2013111), and a grant from Scandiatriplant.

Availability of data and materials

The data generated and analyzed during the current study are not publicly available due to Norway's strict guidelines for privacy policy and data sharing.

Ethics approval and consent to participate

All participants provided written informed consent prior to inclusion. The study was approved by the regional ethic committees in Norway, Sweden and Denmark. The study is conducted according to the Helsinki Declaration. <https://clinicaltrials.gov/> identifier NCT01796379.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Received: 5 September 2019 Accepted: 11 August 2020

Published online: 17 August 2020

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Additional file 1

Figures showing correlations between self-reported physical function and muscle strength in the high-intensity interval training group and the moderate intensity continuous training group at 11 weeks and 1 year after heart transplantation.

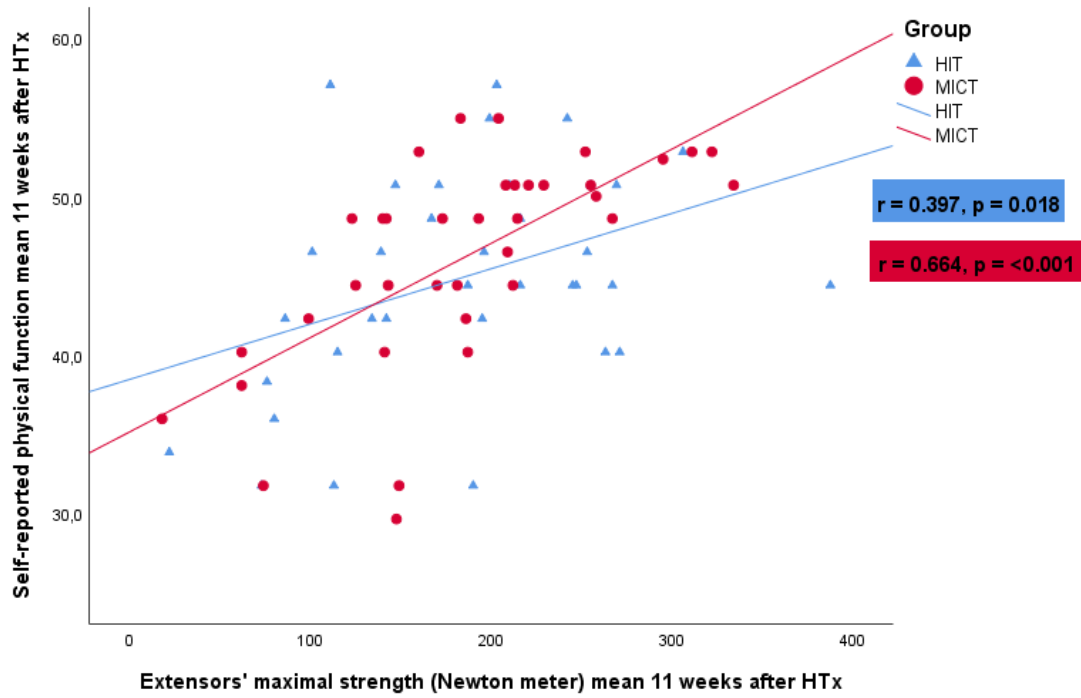
Additional Figure 1. Correlation between self-reported physical function and maximal muscle strength in the high-intensity training group and the moderate intensity continuous training group 11 weeks after heart transplantation (HTx).

Additional Figure 2. Correlation between self-reported physical function and maximal muscle strength in the high-intensity training group and the moderate intensity continuous training group 1 year after heart transplantation (HTx).

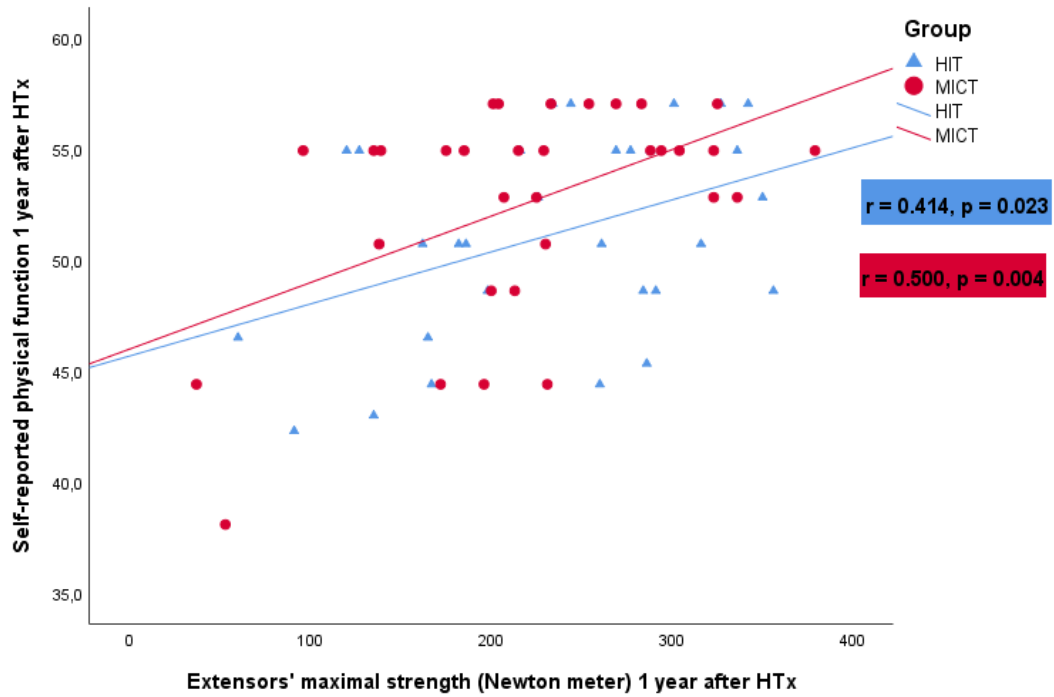
Additional Figure 3. Correlation between self-reported physical function and muscle endurance in the high-intensity training group and the moderate intensity continuous training group 11 weeks after heart transplantation (HTx).

Additional Figure 4 Correlation between self-reported physical function and muscle endurance in the high-intensity training group and the moderate intensity continuous training group 1 year after heart transplantation (HTx) .

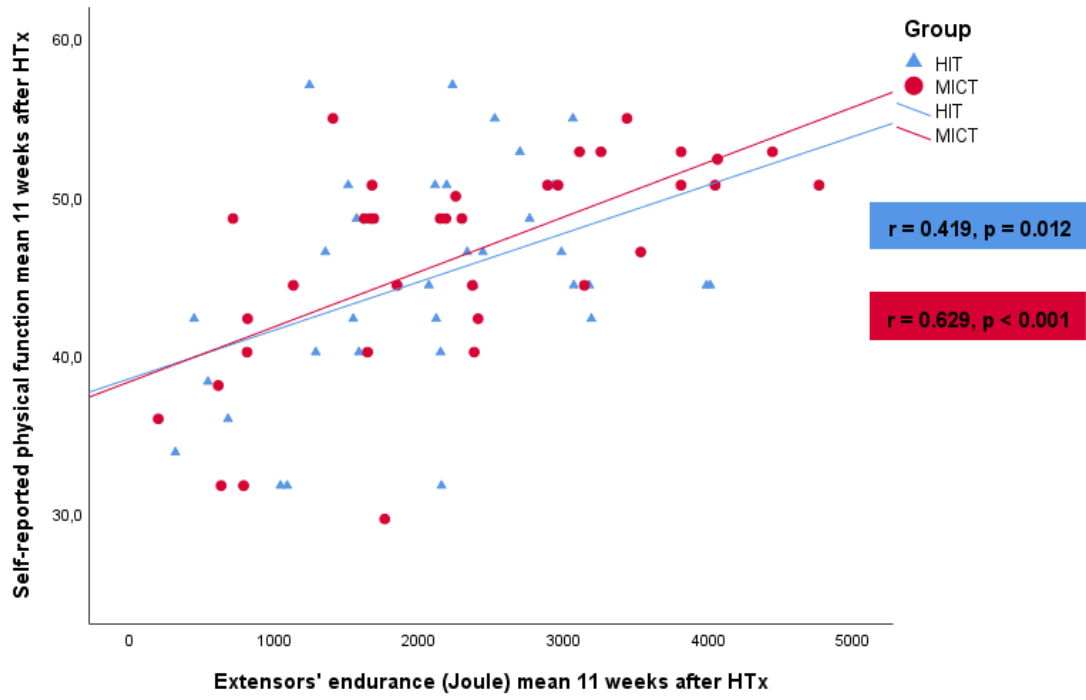
Additional Figure 1



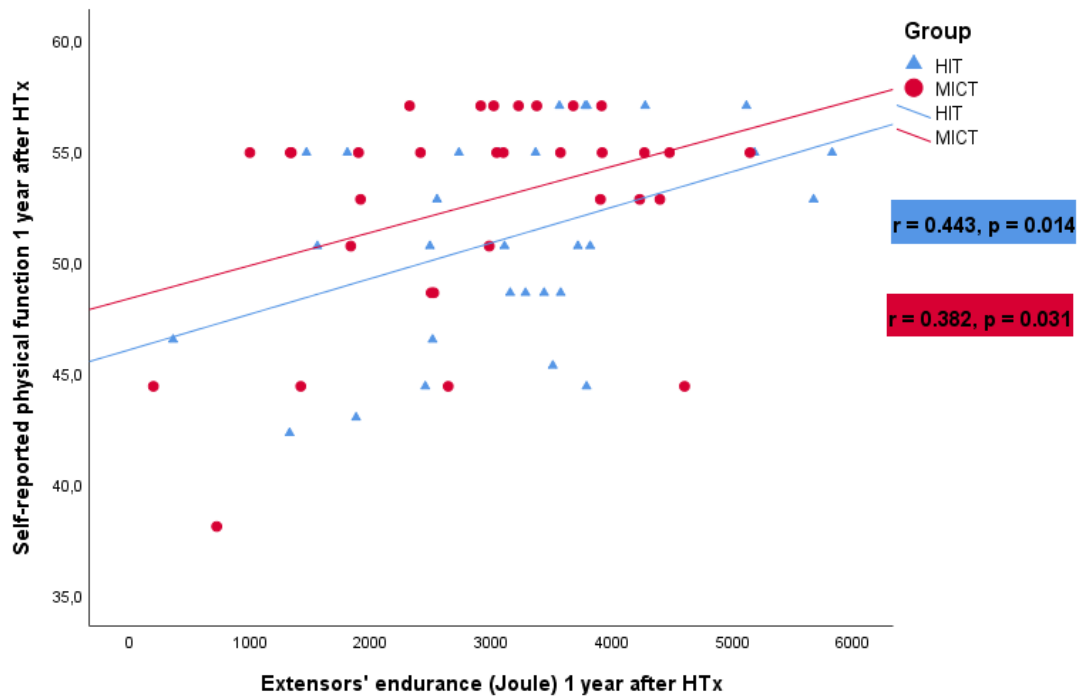
Additional Figure 2



Additional Figure 3



Additional Figure 4





ORIGINAL ARTICLE

Long-term effects of high-intensity training vs moderate intensity training in heart transplant recipients: A 3-year follow-up study of the randomized-controlled HITTs study

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Funding information

The South- Eastern Norway Regional Health Authority, Grant/Award Number: 2013111; The Norwegian Health Association, Grant/Award Number: 12906

The randomized controlled High-Intensity Interval Training in De Novo Heart Transplant Recipients in Scandinavia (HITTs) study compared 9 months of high-intensity interval training (HIT) with moderate intensity continuous training in de novo heart transplant recipients. In our 3-year follow-up study, we aimed to determine whether the effect of early initiation of HIT on peak oxygen consumption (VO_{2peak}) persisted for 2 years postintervention. The study's primary end point was the change in VO_{2peak} (mL/kg/min). The secondary end points were muscle strength, body composition, heart rate response, health-related quality of life, daily physical activity, biomarkers, and heart function. Of 78 patients who completed the 1-year HITTs trial, 65 entered our study and 62 completed the study tests. VO_{2peak} increased from baseline to 1 year and leveled off thereafter. During the intervention period, the increase in VO_{2peak} was larger in the HIT arm; however, 2 years later, there was no significant between-group difference in VO_{2peak} . However, the mean change in the anaerobic threshold and extensor muscle endurance remained significantly higher in the HIT group. Early initiation of HIT after heart transplantation appears to have some sustainable long-term effects. Clinical trial registration number: NCT01796379.

KEYWORDS

allied health, cardiology, clinical research, dysfunction, heart (allograft) function, heart transplantation, nursing, practice, quality of life (QoL), rehabilitation

1 | INTRODUCTION

Heart transplantation (HTx) is a well-established treatment for selected patients with severe heart failure.¹ The survival rate post-HTx

has increased over time, and the median survival in 2019 has been reported to be 12.5 years, and to be 14.8 years for those surviving beyond the first year.² Exercise capacity measured using peak oxygen consumption (VO_{2peak}) is associated with survival,³ and the

Abbreviations: AT, anaerobic threshold; CPET, cardiopulmonary exercise test; HADS, Hospital Anxiety and Depression Scale; HIT, high-intensity interval training; HITTs, High-Intensity Interval Training in De Novo Heart Transplant Recipients in Scandinavia; HRQoL, health-related quality of life; HTx, heart transplantation; HUNT, Nord-Trøndelag Health; METS, Metabolic equivalents; MICT, moderate intensity continuous training; PA index, physical activity index; PA, physical activity; RER, respiratory exchange ratio; SD, standard deviation; SF-36v2, Short Form-36 version 2; TEX, transplant exercise; VAS, visual analogue scale; VO_{2peak} , peak oxygen consumption.

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positive effects of exercise-based cardiac rehabilitation post-HTx have been well documented.^{4,5} Two recent reports have reviewed the benefits of high-intensity interval training (HIT) on cardiovascular health in the healthy population⁶ and in clinical populations.⁷ In short-term follow-up studies (≤ 1 year), HIT has been found to be more effective than moderate intensity continuous training (MICT) in increasing VO_{2peak} in de novo HTx recipients⁸ and in maintenance HTx recipients.^{4,9} Positive associations between early cardiac rehabilitation and long-term survival¹⁰ and between early rehabilitation and a decrease in readmissions during the first year following HTx have also been reported.¹¹

Only one randomized-controlled long-term (5 years) follow-up trial has studied the effects of HIT vs control (no specified training) on exercise capacity in HTx recipients.¹² In that study, no differences were found between the two groups in terms of VO_{2peak} 4 years postintervention. However, there was a significantly lower burden of anxiety in the HIT group, suggesting that HIT has long-term positive effects on symptoms of anxiety in this patient group.¹²

In the recently published High-Intensity Interval Training in De Novo Heart Transplant Recipients in Scandinavia (HITTS) trial, we assessed exercise capacity 9 months after randomly assigning patients to HIT or MICT just 3 months after HTx.⁸ In this report, we present the 3-year follow-up data from these patients. Between the 1- and 3-year follow-up, no systematic exercise intervention or formal training instructions were applied. We aimed to investigate the long-term effects of HIT vs MICT on VO_{2peak} , muscle strength, pulmonary function, daily physical activity (PA), health-related quality of life (HRQoL), symptoms of depression and anxiety, biomarkers, and heart function in de novo HTx recipients.

2 | METHODS

The methods used in the HITTS trial have been described previously.^{8,13} In our study, medically stable HTx recipients were randomly allocated to HIT or MICT in a 1:1 fashion, on average 3 months after HTx. Prior to randomization, we performed baseline tests. The participants in both groups (HIT, $n = 37$; and MICT, $n = 41$) then followed a rigorous 9-month training program, with a combination of aerobic exercise (HIT vs MICT) and resistance training. All exercise sessions from baseline to 1-year follow-up were performed in each participant's local community, led by a physical therapist near the participant's home. The local physical therapist had direct access to the leading in-hospital physical therapist and could discuss the progression or ask questions during the intervention period. This method is a decentralized rehabilitation model with close cooperation between the local physical therapist and the physical therapist at the transplant center. The baseline tests were repeated after 9 months of intervention, approximately 1-year post-HTx, defined as the 1-year follow-up. After the first year and up to the 3-year follow-up, the participants were not assigned to a specific exercise regimen but were encouraged to continue to exercise and were recommended to perform various activities at different intensities (Figure 1).

Due to limited resources, only participants from Norway were included in the HITTS 3-year follow-up (3 years post-HTx) (Figure 2). The study was approved by the South-East Regional Committee in Norway (Approval number 2012/2305) and all participants gave their informed consent prior to inclusion. At baseline (3 months post-HTx), at the end of the intervention period (1-year follow-up), and at the 3-year follow-up, participants underwent a cardiopulmonary exercise test (CPET), muscle strength

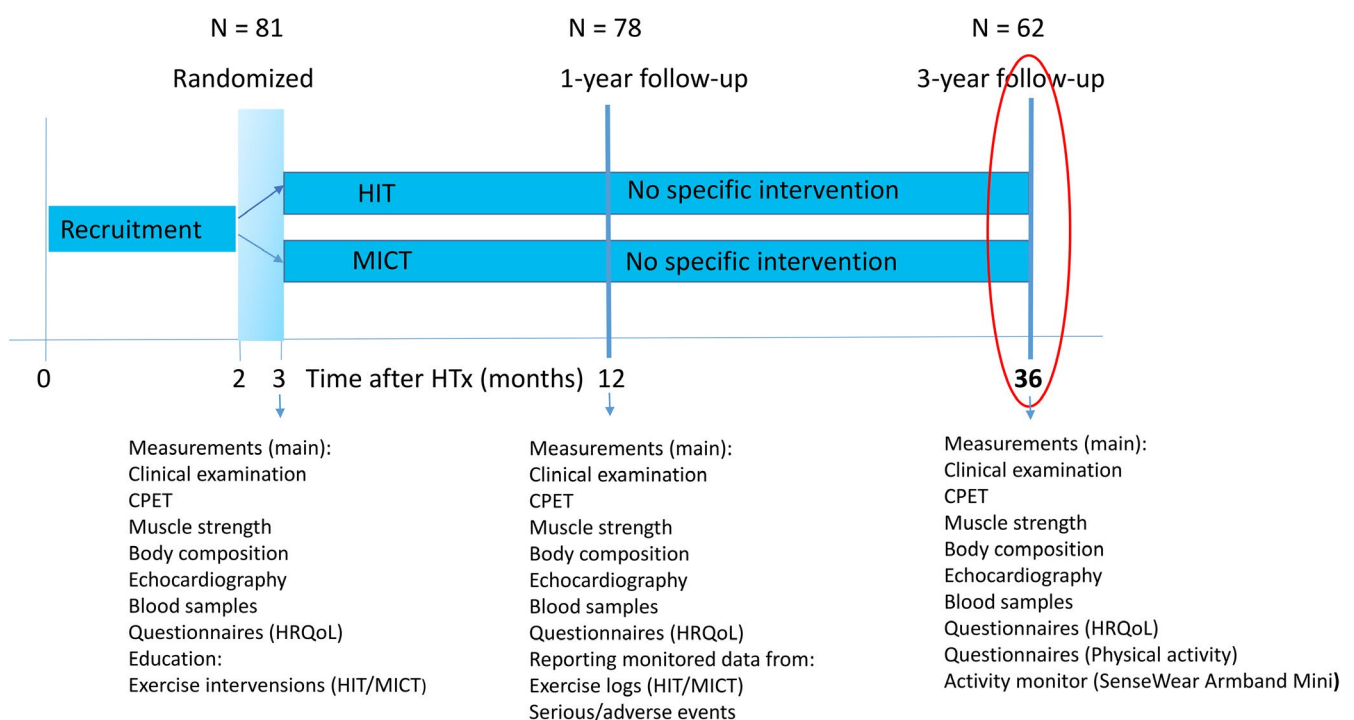
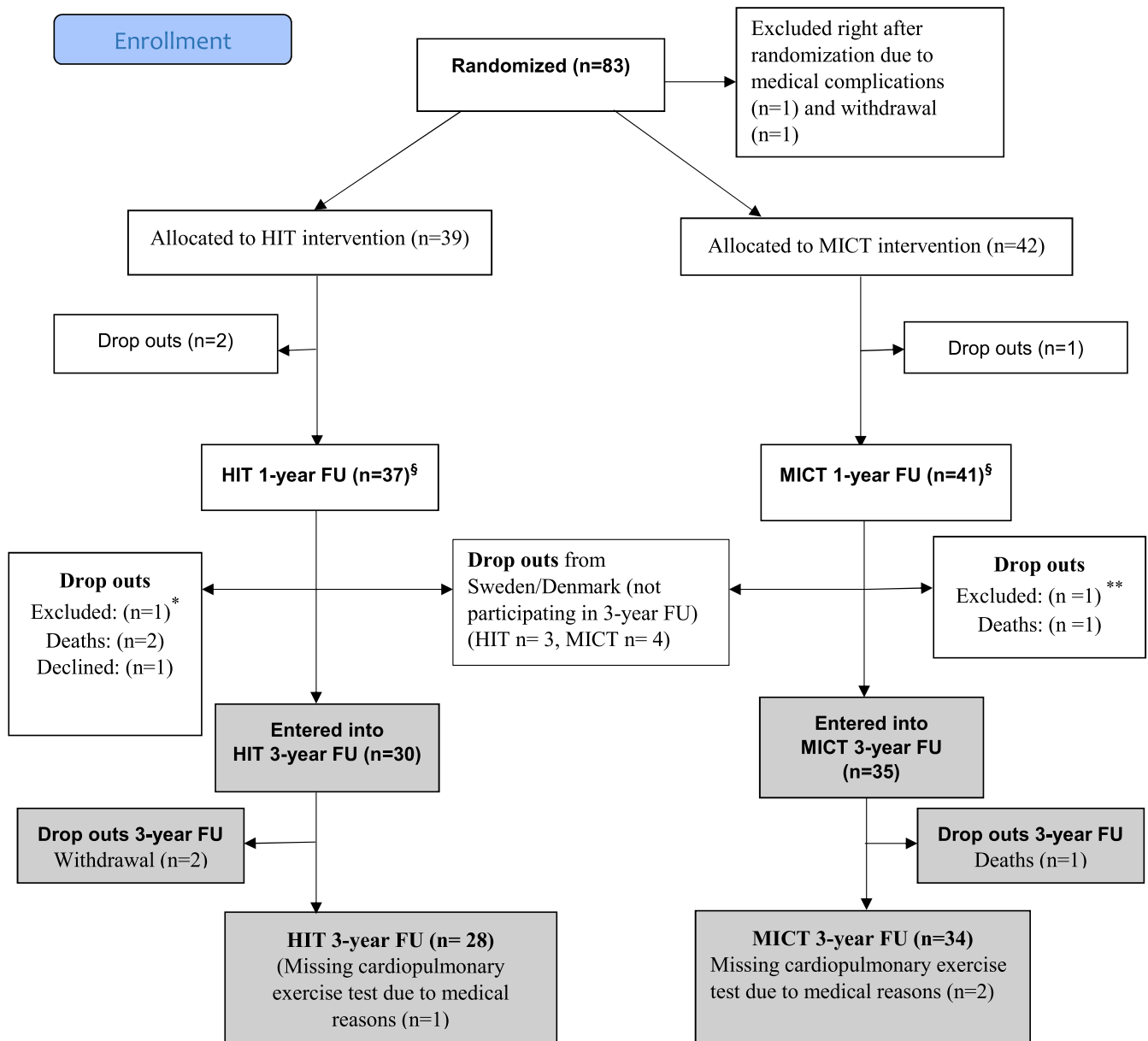


FIGURE 1 Design of the HITTS study [Color figure can be viewed at wileyonlinelibrary.com]



§Data from the 1-year follow is previously published in *Circulation* (2019) Nytrøen K, Rolid K, Andreassen AK, et al. Effect of High-Intensity Interval Training in De Novo Heart Transplant Recipients in Scandinavia: 1-Year Follow-Up of the HITTS Randomized, Controlled Study. *Circulation*. 2019;139(19):2198-2211.

Participants enrolled in the 3-year follow-up study are highlighted in grey.

Reasons for excluded from 3-yr follow-up: *Hospitalized due to psychiatric issues (n=1) **On re-transplantation waiting list (n=1).

FIGURE 2 Enrollment in the HITTS study [Color figure can be viewed at wileyonlinelibrary.com]

tests, blood sampling, echocardiography, and measurements of body composition, and they completed HRQoL questionnaires, which included questions relating to symptoms of depression and anxiety. PA was measured using activity monitors and questionnaires at the 3-year follow-up.

2.1 | Exercise testing

Participants underwent a CPET, using a breath-by-breath method, on either a treadmill (Jaeger Masterscreen; Carefusion; Hoehberg, Germany) or on a bicycle (Schiller Cardiovit CS-200 Excellence, Baar,

Switzerland), as described previously.^{8,13,14} The treadmill test-protocol was a ramp protocol with a constant speed and a gradually increasing inclination (2% every 2 minutes).¹⁵ Pulmonary function was assessed using spirometry prior to the CPET.

2.2 | Muscle strength testing

Bilateral isokinetic maximal muscle strength and muscle endurance in the quadriceps femoris and the hamstring muscles were measured with a dynamometer (Cybex 6000, Lumex, Ronkonkoma, NY). Maximal muscle strength was performed with five repetitions at an angular velocity of 60°/s and the mean peak value was calculated in Newton meters (Nm). Muscle endurance was tested with 30 repetitions at 240°/s and the total work (the sum of all repetitions) in Joules (J) was calculated.^{16,17} The participants were tested in a seated position, with the right and left legs tested consecutively.

2.3 | Blood samples

Blood samples were obtained the morning prior to exercise testing, as described elsewhere.^{8,14}

2.4 | Body composition

Body composition was determined prior to the exercise testing using bioelectrical impedance analysis with Tanita InnerscanV model BC-545N (Tanita, Arlington, Heights, IL).^{14,18}

2.5 | Activity monitor

Immediately following the 3-year follow-up, the participants were instructed to wear a SenseWear Armband Mini (BodyMedia, Inc Smithfield Street, Pittsburgh, PA)¹⁹ for 7 days for quantification of their daily PA. This armband is a three-axis accelerometer that has been validated previously for use in adults.²⁰ It has also been used previously in cardiac rehabilitation²¹ and in a study involving HTx recipients from this study group.¹²

Minutes of daily activity at an intensity of three metabolic equivalents (3 METs) were recorded. We also categorized and reported minutes of activity at different intensities: sedentary (<1.5 METs), light (1.5-2.9 METs), moderate (3.0-5.9 METs), vigorous (6.0-9.0 METs), and very vigorous (>9.0 METs).

2.6 | Self-reported physical activity

Self-reported PA was quantified using a questionnaire adopted from the Nord-Trøndelag Health Study (the HUNT study),²² and we used the HUNT 3 questionnaire. This questionnaire mapped the intensity,

frequency, and duration of PA. The answers were coded according to that in the study by Kurtze et al²³ (codes in parentheses): (i) Frequency: never (0), less than once a week (0.5), once a week (1), 2-3 times per week (2.5), almost every day (5); (ii) Intensity: easy, no sweating or breathlessness (1), pushing hard, becoming breathless and sweaty (2), pushing to near exhaustion (3), and; (iii) Duration: <15 minutes (0.10), 15-29 minutes (0.38), 30-60 minutes (0.75), and >1 hour (1). To calculate the product of intensity, frequency, and duration, we used a previously validated and reliable PA index score.²³

Questions concerning time spent in a seated position (hours per day) and time spent on daily PA at work and at leisure were included.

2.7 | Health-related quality of life (HRQoL)

HRQoL was reported using the Short Form-36 version 2 (SF-36v2).²⁴ We transformed the SF-36v2 scores into norm-based scores of 50 ± 10 (mean \pm standard deviation [SD]) as recommended for this version.²⁴ Symptoms of depression and anxiety were measured using the Hospital Anxiety and Depression Scale (HADS).²⁵ The HADS score was calculated according to 2 separate scales, namely, HADS-A for symptoms of anxiety and HADS-D for symptoms of depression. A cut-off value ≥ 8 represented symptoms of anxiety and/or depression on both scales.^{25,26} Participants also reported how participation in the HITTS study had contributed to their general health and well-being, using a visual analogue scale (VAS).

2.8 | Statistical analysis

All analyses were performed with SPSS (IBM SPSS Statistics for Windows, Version 25.0; IBM Corp, Armonk, NY). To analyze differences between the groups, independent T-tests or Mann-Whitney *U* tests were used for continuous variables, whereas Pearson's chi-square or Fisher's exact tests were used for categorical data. For within-group changes in continuous variables, a paired T-test or a Wilcoxon signed-rank test was performed. Analyses were checked for normality, interaction, and homogeneity of variances. We dichotomized variables on PA and data from the SenseWear Armband, where appropriate. The level of statistical significance was set at *P*-values < .05 and all tests were two sided.

3 | RESULTS

In total, 78 patients completed the core study (1-year follow-up). Sixty-five patients, all from Norway, entered the 3-year follow-up study, and of these, 62 (95%) completed the 3-year follow-up (Figure 2 flow-chart). Mean age \pm standard deviation [SD] was 52 ± 13 and 76% were men. At 3-year follow-up there were no differences in clinical characteristics between patients originally allocated to the HIT and MICT groups (Table 1). During 3-years of follow-up,

TABLE 1 Clinical characteristics at 3-year follow-up divided in groups^a

Variable	High-intensity interval training (HIT) (n = 28), mean ± SD	Moderate intensity continuous training (MICT) (n = 34), mean ± SD
Sex n (%) (men)	21 (75)	26 (77)
Age (years)	53 ± 11	51 ± 14
Donor age (years)	36 ± 14	37 ± 14
Ischemic time (min)	176 ± 74	181 ± 84
Smokers (n (%) No/Ex-smoker)	18 (64)/10 (36)	16 (50)/16 (50)
Medication (n (%) Yes)		
Cyclosporine	14 (56)	20 (59)
Tacrolimus	5 (18)	6 (18)
Everolimus	9 (32)	11 (32)
Prednisolone	28 (100)	33 (97)
Mycophenolate	24 (86)	30 (88)
Azathioprine	1 (4)	2 (7)
Ezetimibe	3 (11)	1 (3)
Statins	27 (96)	32 (94)
Beta blockers	12 (43)	10 (29)
Calcium blockers	8 (29)	7 (21)
ACE inhibitors	2 (7)	2 (6)
ARB	6 (21)	8 (24)
Diuretics	12 (43)	16 (47)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

Note: Data are numbers (%) or mean with standard deviation ± SD. Compared to baseline fewer participants were treated with cyclosporine and diuretics, whereas a slightly higher number were treated with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers at 3-year follow-up.

^aNo difference between groups.

the number of patients who used diuretics and/or cyclosporine was reduced, whereas the number of patients using angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers increased (data not shown).

At 3 years, there were no differences between the two groups in terms of the amount of daily PA. In the HIT group, 79% of participants vs 82% of participants in the MICT group exercised for ≥2 times per week. Most participants were exercising at moderate intensity (HIT group, 69% vs MICT group, 66%). A few participants in both groups reported that they were “pushing to near exhaustion” in response to questions concerning exercise intensity (HIT group, n = 3; MICT group, n = 4).

Moreover, a high number of participants in both groups performed at least 30 minutes of daily PA at work and/or in their leisure

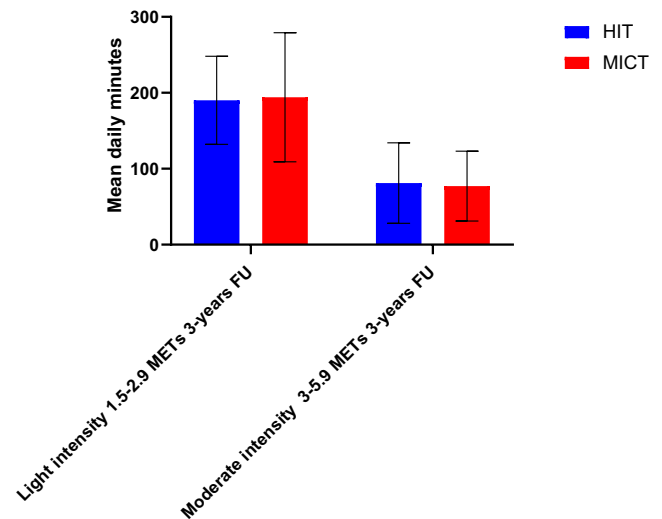


FIGURE 3 Activity monitor. Mean minutes of daily physical activity broken down to light and moderate intensity. Comparisons between groups at 3-year follow-up [Color figure can be viewed at wileyonlinelibrary.com]

time, 85% in the HIT group vs 91% in the MICT group. Sedentary time reported as hours spent sitting daily was 6 ± 2 hours in the HIT group and 7 ± 2 hours in the MICT group.

Data from the activity monitors showed that participants in both groups were undertaking moderate PA (≥3.0-5.9 METs) >30 minutes daily (HIT group, 81 ± 53 minutes; MICT group, 78 ± 46 minutes) (Figure 3).

3.1 | Maximal exercise capacity

Results of the physical exercise tests are shown in Table 2. There were no differences between the two groups from 1-year follow-up to 3-year follow-up (after the intervention period). The exercise capacity remained stable with a small decline in VO_{2peak} in both groups: -0.3 mL/kg/min in the HIT group vs -0.9 mL/kg/min in the MICT group (P for difference = .497) (Figure 4). Thus, although the change in VO_{2peak} from baseline to 1 year was significantly higher in the HIT group,⁸ there was no significant between-group difference in the change in VO_{2peak} from baseline to 3 years (Table 2, Figure 4).

Respiratory exchange ratio (RER) and rated perceived exertion (RPE) peak levels from baseline to the 3-year follow-up did not differ between groups (Table 2). There were significant correlations between the PA index and the activity monitor (≥3.0-5.9 METs) (Spearman's rho 0.375, $P < .05$) and between VO_{2peak} and the activity monitor (Pearson's r 0.511, $P < .001$).

3.2 | Submaximal exercise

The HIT group showed a significantly higher mean change in the anaerobic threshold (AT) from baseline to 3-year follow-up than the

TABLE 2 Group comparisons of exercise capacity

Variable	High-intensity interval training (HIT)		Moderate intensity continuous training (MICT)		Mean difference between groups [95% CI]	t test P value
	Baseline (mean 11 weeks after HTx)	3-year follow-up	Baseline (mean 11 weeks after HTx)	3-year follow-up		
CPET						
VO _{2peak} (mL/kg/min)	19.7 ± 4.6	24.0 ± 6.8**	21.6 ± 5.44	24.1 ± 8.3*	1.7 [-0.73, 4.21]	.163
% of predicted	55 ± 12	67 ± 16**	58 ± 13	65 ± 20*	5.1 [-1.7, 12.0]	.140
VO _{2peak} (L/min)	1.50 ± 0.40	2.04 ± 0.62**	1.67 ± 0.44	2.01 ± 0.64**	0.2 [-0.0003, 0.397]	.053
Respiratory exchange ratio	1.18 ± 0.11	1.15 ± 0.07	1.22 ± 0.13	1.17 ± 0.09	0.01 [0.3, -0.05]	.653
Borg scale	18.6 ± 0.5	18.9 ± 0.5*	18.5 ± 1.1	18.4 ± 0.91	0.4 [-0.2, 1.0]	.186
Test duration (min)	9.3 ± 2.4	14.3 ± 4.5**	10.1 ± 3.1	13.1 ± 4.7**	1.9 [-0.02, 3.9]	.053
O ₂ pulse (mL/beat)	11.8 ± 3.3	13.4 ± 3.6*	13.2 ± 3.6	13.4 ± 4.0	1.4 [-0.2, 9.3]	.087
VE max (L)	70.0 ± 21.0	84.2 ± 27.4**	75.6 ± 25.8	84.9 ± 29.6*	5.0 [-5.8, 15.7]	.336
VE/VCO ₂ slope	34.1 ± 6.8	31.3 ± 4.4*	34.8 ± 7.6	31.4 ± 6.3*	-2.2 [-5.3, 0.9]	.166
AT (L/min)	1.00 ± 0.29	1.35 ± 0.48*	1.14 ± 0.35	1.22 ± 0.46	0.3 [0.04, 0.5]	.024
AT @ percent of VO _{2peak}	65.8 ± 12.3	65.2 ± 16.6	68.3 ± 13.3	61.7 ± 16.6*	5.9 [-4.3, 16.2]	.593
Chronotropic responses						
Peak HR	127.4 ± 17.5	150.3 ± 19.3**	127.5 ± 22.4	149.7 ± 23.8**	0.7 [-8.3, 9.6]	.882
% HR max	75.2 ± 11.9	90.7 ± 12.2	74.2 ± 13.2	88.3 ± 13.2	1.4 [-3.7, 6.4]	.591
HR reserve (beats/min)	41 ± 16	63 ± 19**	43 ± 17	64 ± 22	1.6 [-7.4, 10.6]	.721
Chronotropic response index	0.505 ± 2.09	0.812 ± 0.254**	0.506 ± 0.209	0.795 ± 0.263	0.02 [-0.1, 0.1]	.749
HRR Beats at 2 min	-1 ± 5	-25 ± 13**	-0.2 ± 8	-27 ± 13**	2.6 [-4.9, 10.01]	.492

(Continues)

TABLE 2 (Continued)

	High-intensity interval training (HIT)	Moderate intensity continuous training (MICT)	Mean difference between groups [95% CI]	t test P value
Muscular capacity				
Maximal muscle strength extensors (Newton meter)	172 ± 59	188 ± 75	25.6 [-1.6, 52.7]	.064
Muscle endurance extensors (Joule)	2069 ± 897	2308 ± 1247	591.8 [44.4, 1139.0]	.035
Maximal muscle strength flexors (Newton meter)	88 ± 53	76 ± 57	16.1 [-5.4, 38.2]	.136
Muscle endurance flexors (Joule)	864 ± 658	897 ± 826	415 [23.5, 806]	.038

Abbreviations: AT, anaerobic threshold; CI, confidence interval; CPET, cardiopulmonary exercise test; HR, heart rate; HRR, heart rate recovery; O₂, oxygen; VEmax, maximum ventilation; VE, ventilation; VCO₂, carbon dioxide production.

Note: Data are mean with standard deviation ± SD.

*Within-group differences $P < .05$.

**Within-group differences $P < .001$.

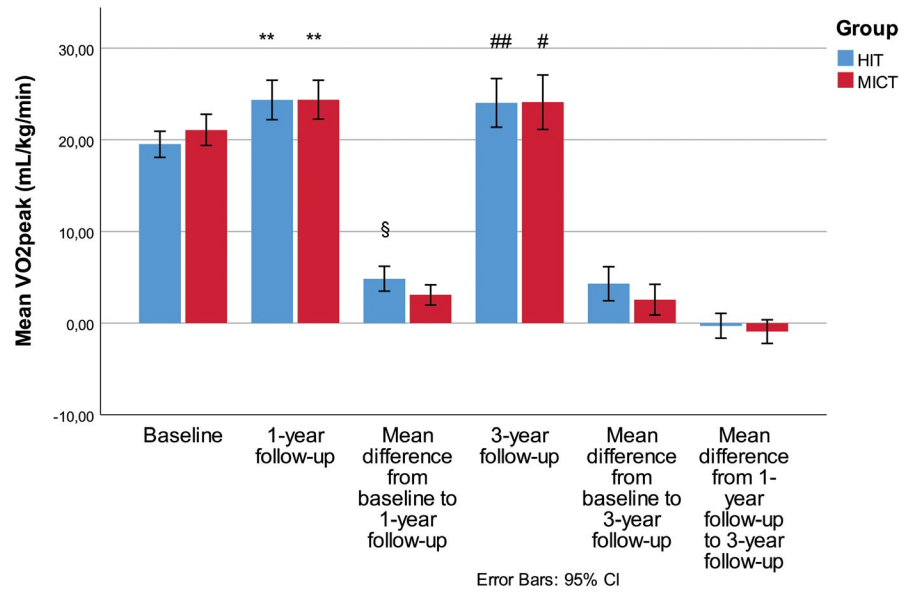


FIGURE 4 Mean VO_{2peak} comparison of high-intensity interval training (HIT) group vs moderate intensity continuous training (MICT) group. **Within-group difference from baseline to 1-year follow-up $P < .001$. §Between-group difference from baseline to 1-year follow-up $P < .05$. ##Within-group difference from baseline to 3-year follow-up $P < .001$, # $P < .05$ [Color figure can be viewed at wileyonlinelibrary.com]

MICT group, and the between-group mean difference was significant ($P = .024$) (Table 2).

protein, estimated glomerular filtration rate, and hemoglobin) from baseline to the 3-year follow-up (Table 3).

3.3 | Muscle strength

Muscle endurance improved significantly in both groups from baseline to 1-year follow-up, with a significantly higher between-group change in the HIT group. This finding remained significant from baseline to 3-year follow-up (Table 2, Figure 5).

3.5 | Health-related quality of life (HRQoL)

The median values of the physical and mental component summary scores from the SF-36v2 were >50 in both groups. Both groups had a significant within-group change from baseline to 3-year follow-up in the physical summary scores, while the mental summary scores remained high and stable during the 3 years of follow-up (Table 3). The physical summary scores 3 years post-HTx were in line with those reported for age- and sex-adjusted values from the U.S. general population, whereas the mental summary scores were above those of the U.S. general population.²⁴

3.4 | Other parameters

There were no differences between the two groups in terms of changes in body composition, lung function, heart function, or biomarkers (high- and low-density lipoproteins, triglycerides, cardiac troponin T, N-terminal pro-brain natriuretic peptide, C-reactive

The between-group differences from baseline to the 3-year follow-up concerning both HADS-A and HADS-D were not significant (HADS-A, $P = .925$; HADS-D, $P = .350$). Only 7% of patients in the HIT group vs

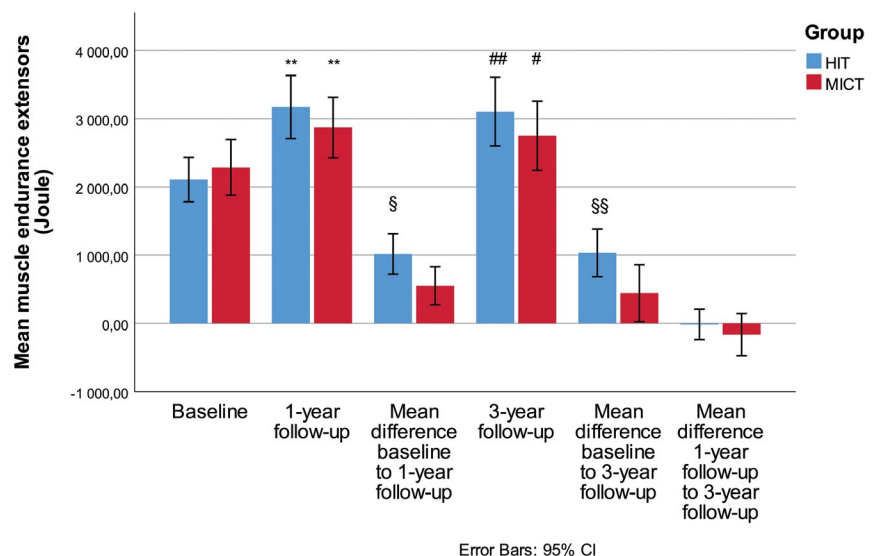


FIGURE 5 Mean muscle endurance extensors' comparison of high-intensity interval training (HIT) group vs moderate intensity continuous training (MICT) group. **Within-group difference from baseline to 1-year follow-up $P < .001$. ##Within-group difference from baseline to 3-year follow-up $P < .001$, # $P < .05$. §Between-group difference from baseline to 1-year follow-up $P < .05$. §§Between-group difference from baseline to 3-year follow-up $P < .05$ [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Group comparisons of pulmonary function, heart function, blood pressure, body composition, blood samples, and health-related quality of life

Variable	High-intensity interval training (HIT)		Moderate intensity continuous training (MICT)		Mean difference between groups [95% CI]	t test P value
	Baseline	3-year follow-up	Baseline	3-year follow-up		
Spirometry						
PEF (%)	80 ± 21	87 ± 21 [*]	86 ± 24	87 ± 22	6.9 [-16, 2.4]	.144
FEV1 (%)	76 ± 14	87 ± 17 ^{**}	84 ± 18	94 ± 19 ^{**}	0.3 [-4.9, 5.4]	.921
Blood pressure (mm Hg)						
24 h overall SBP	131 ± 10	132 ± 15	133 ± 13	131 ± 14	2.4 [-5.8, 10.6]	.561
24 h overall DBP	80 ± 5	80 ± 9	81 ± 8	81 ± 9	0.1 [-4.7, 5.0]	.954
24 h overall heart rate	92 ± 10	94 ± 14	87 ± 10	89 ± 9	0.04 [-6.1, 6.2]	.990
Body composition						
Weight (kg)	76.6 ± 13.6	85.2 ± 17.3 ^{**}	78.1 ± 16	84 ± 17.7 ^{**}	2.5 [-1.8, 6.7]	.251
Body mass index	24.6 ± 2.9	27.4 ± 4.0 ^{**}	25.4 ± 4.0	27.5 ± 4.3	0.7 [-0.7, 2.0]	.320
Body fat (%)	24.0 ± 7.7	28.5 ± 9.8 [*]	24.4 ± 9.6	27.6 ± 9.4 [*]	1.21 [-1.9, 4.3]	.438
Muscle mass (kg)	54.7 ± 10.0	57.6 ± 11.1 ^{**}	56.3 ± 11.1	58.5 ± 11.3 [*]	-1.9 [-7.3, 3.5]	.486
Biomarkers						
Hemoglobin (g/dL)	11.6 ± 1.8	13.9 ± 1.1 ^{**}	11.9 ± 1.3	13.9 ± 1.8 ^{**}	0.3 [-0.5, 1.1]	.438
eGFR (mL/min/1.73 m ²)	62.4 ± 20.0	69.2 ± 18.5	62.7 ± 21.5	74.4 ± 21.2 ^{**}	-5 [-14.4, 4.5]	.300
hs-CRP (mg/L) (median (IQR))	3.0 (6.9)	2.6 (5.1)	2.2 (6.0)	2.0 (5.0)		.291 ^a
hs-Troponin T (ng/L) (median (IQR))	35.5 (47.5)	13.0 (13.0)	36.5 (42)	11.0 (13)		.699 ^a
NT-proBNP (ng/L) (median (IQR))	1019 (1250) ^{**}	238 (217)	968 (850)	209 (273) ^{**}		.745 ^a
LDL (mmol/L)	3.2 ± 1.0	2.9 ± 0.8	2.7 ± 0.8	2.8 ± 1.0	-0.3 [-0.8, 0.2]	.243
HDL (mmol/L)	1.5 ± 0.5	1.6 ± 0.5	1.5 ± 0.5	1.5 ± 0.5	0.02 [-0.1, 0.2]	.847
TG (mmol/L)	2.4 ± 1.3	2.1 ± 0.9	2.1 ± 1.0	2.1 ± 1.3	-0.3 [-1.0, 0.4]	.358
Echocardiography						
HR rest (during echocardiography)	89 ± 9	88 ± 13	85 ± 10	85 ± 10	-1.9 [-7.3, 3.5]	.486
Ejection fraction (%)	55.9 ± 5.6	54.6 ± 5.8	58.3 ± 6.0	57 ± 6.2	0.05 [-4.5, 4.6]	.984
LVEDD (cm)	4.9 ± 0.5	5.0 ± 0.6	4.8 ± 0.4	4.7 ± 0.6	0.2 [-0.12, 0.43]	.263
LVESD (cm)	3.1 ± 0.4	3.2 ± 1.0	3.1 ± 0.4	3.2 ± 0.6	-0.04 [-0.5, 0.4]	.832
Cardiac output (L/min)	6.1 ± 1.3	5.5 ± 0.6 [*]	6.1 ± 1.3	5.6 ± 1.1	-0.1 [-0.9, 0.6]	.731
Health-related quality of life						
VAS scale (0-100 mm)	77 ± 23 [*]	76 ± 21	72 ± 23 ^c	69 ± 22		.215
PCS (median (IQR))	43 (14)	50 (15) [*]	44 (9)	51 (17) [*]		.703 ^a
MCS (median (IQR))	59 (13)	56 (10)	56 (10)	57 (12)		.976 ^a
HADS Anxiety (median (IQR))	2.0 (4.0)	4.0 (4.0)	3.0 (3.0)	3.0 (5.0)		.925 ^a
HADS anxiety score ≥ 8 n (%)	4 (14)	2 (7)	4 (12)	5 (17)		.425 ^b
HADS Depression (median (IQR))	2.0 (4.0)	2.0 (5.0)	1.0 (1.3)	1.0 (3.0)		.350 ^b
HADS depression score ≥ 8 n (%)	3 (11)	1 (4)	0 (0)	2 (6)		1.000 ^b

Abbreviations: CI, confidence interval; CRP, C-reactive protein; DPP, diastolic blood pressure; eGFR, estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration); FEV₁, forced expiratory volume at 1 second; HADS, Hospital Anxiety and Depression Scale; HDL, high-density lipoprotein; HR, heart rate; hs, high-sensitivity; LDL, low-density lipoprotein; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; MCS, mental component summary score from SF-36v2; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCS, physical component summary score from SF-36v2; PEF, peak expiratory flow; SBP, systolic blood pressure; TG, triglycerides; VAS visual analogue scale.

Note: Data are mean with standard deviation ± SD or median with interquartile range (IQR) or numbers (%).

^aMann-Whitney U test.

^bFisher's exact test.

^c1-year follow-up.

*Within-group differences $P < .05$.

**Within-group differences $P < .001$.

17% in the MICT group had a score ≥ 8 on the HADS-A scale, indicating symptoms of anxiety, whereas 4% of patients in the HIT group vs 6% in the MICT reported symptoms of depression 3 years post-HTx (Table 3).

4 | DISCUSSION

This study aimed to determine whether the effect of early initiation (3 months post-HTx) of HIT on VO_{2peak} persisted for 2 years after intervention. Although earlier initiation of HIT resulted in a higher improvement in exercise capacity, we observed no significant sustained effect in favor of HIT. However, the mean change in muscle endurance and AT from baseline to 3 years post-HTx was significantly higher in the HIT group.

In this study, both groups had a clinically meaningful and statistically significant increase in VO_{2peak} during the first year, and the mean change between groups was significantly higher in the HIT group compared to the MICT group at 1-year follow-up.⁸ At 3-year follow-up, VO_{2peak} was still higher than at baseline in both groups, but the mean difference between groups was no longer statistically significant. The exact reasons for this are unclear. We consider that difficulties in maintaining HIT training, resulting in similar levels of activity in both groups, was the most likely explanation. Two years after the intervention, very few participants in this study were found to have undertaken vigorous daily activity (≥ 6 METs) during the week. To perform HIT without supervision and without an encouraging motivator might be a challenge, which is suggested by the low level of vigorous activity observed after the end of the intervention. This explanation is in line with a previous Transplant Exercise (TEX) study, where a sustained effect on VO_{2peak} could not be maintained during 5-years of follow-up.¹²

Despite the exercise regimens, participants in both groups gained weight; both muscle mass and body fat, with a corresponding increase in body mass index. This is commonly seen in daily practice and underscore the challenges related to weight gain in the HTx populations.²⁷

Only a small, nonsignificant decline in VO_{2peak} mL/kg/min was observed from the end of the intervention period up to the 3-year follow-up (a 2.6% decline for the total population). An age-related decline in VO_{2peak} can be expected in a healthy population.^{28,29} A decline of approximately 10% and 15% per decade in the 40-49 year and 50-59 year age groups, respectively, has been reported.²⁸ More recent data have shown a 9% average decline in VO_{2peak} per decade, with a smaller decrease in men than in women.³⁰ The significant mean difference in muscle endurance between the HIT and MICT groups observed 3 years post-HTx is in line with previous findings of favorable effects of HIT on peripheral factors.^{8,31} This is the first study to show significant long-term effects of HIT compared to MICT on muscle endurance. In the TEX study,¹² no difference was found in muscle endurance between the HIT and the control groups at 5-year follow-up in maintenance HTx recipients. The findings in this study suggest that early initiation of exercise, especially HIT, resulted in superior effects on muscular

exercise capacity, compared to those of exercise initiated at a later date. Yardley et al³² reported a trend toward increased angiogenesis after HIT compared to MICT, but the precise mechanism in relation to the peripheral muscular effects remains to be determined.

In the present study, the AT was higher for participants in the HIT group than for those in the MICT group. This finding was consistent with results reported by Nytrøen et al,³¹ who found that compared to the control group, the HIT group had a decreased RER and heart rate during submaximal exercise intensities, suggesting favorable effects of HIT on work efficacy in maintenance HTx recipients.

In this study, both groups exercised more than the median exercise level observed in a healthy population in Norway (data derived from the HUNT study).³³ The effects of being involved in a long-term exercise study, with information and weekly supervision, may alter participants' lifestyles and PA routines in an especially beneficial way and facilitate a long-lasting active and healthy lifestyle.^{34,35} The decentralized rehabilitation model used in this study might have been particularly important in encouraging social support from the family and also in allowing participants to become confident with exercising outside the hospital. In addition, decentralized training is cost-effective and less resource-demanding compared to in-hospital exercise, and it allows for a longer-lasting and more continuous rehabilitation period.

In keeping with other long-term follow-up studies that have demonstrated a high and stable HRQoL from 3 up to 18 years post-HTx,^{36,37} our findings indicated that the participants' HRQoL in both groups remained high 3 years post-HTx. The physical component summary scores in this follow-up study were similar to those of the general population,²⁴ which was in contrast to the findings of a non-exercise longitudinal study by Saeed et al.³⁶

The low proportions of symptoms of depression and anxiety found in both groups in this study contrast the higher previously reported cumulative rate of 25% for depression and 17% for anxiety 3 years post-HTx.³⁸

4.1 | Strength and limitations

The main strengths of this study are the randomized-controlled study design, the decentralized intervention arms, the long duration of the intervention, and the long-term follow-up. Few randomized long-term follow-up exercise studies have been undertaken, and this is the first exercise study to follow-up a de novo HTx cohort for >1 year. It is also the first study to have introduced early HIT post-HTx. Another strength is the comprehensive assessment of exercise capacity and PA, using a combination of self-reported, validated questionnaires and objective methods (CPET and activity monitors). A large proportion of the participants completed the 3-year follow-up. Nonetheless, the limited number of patients may have hindered the detection of subtle between-group differences. A major limitation of the present study is the lack of a nonexercising control group. However, since the health-promoting effects of cardiac rehabilitation in HTx recipients was described in 1999,³⁹

cardiac rehabilitation has become standard in many institutions, including ours. We therefore found the inclusion of a third nonexercising arm impossible due to ethical considerations. Nevertheless, from two of our previous reports, we demonstrate that lower VO_{2peak} at the time cardiac rehabilitation was not standard⁴⁰ compared to a recent cohort where exercise had become part of the general rehabilitation program (yet without a formal protocol)^{41,42} (Table S1). We believe that subsequent studies should focus on how a high adherence to HIT could be maintained, perhaps with shorter exercise bouts.

The high level of PA in both groups documented by patients' self-report and by activity monitors in this study might also be a result of social desirability bias.⁴³

The study's inclusion criteria may have influenced the low rates of participants with symptoms of depression and anxiety, as only medically stable patients were eligible.

Finally, the single-center design of the 3-year follow-up of the HITTS study limits the generalizability compared to a multicenter study.

5 | CONCLUSIONS

Early allocation to HIT post-HTx did not result in sustained improvement at 3-year follow-up in VO_{2peak} , compared to allocation to MICT. However, we observed significant differences between the groups in muscle endurance and AT in favor of the HIT group 3 years post-HTx. With a high proportion in both groups still performing PA for at least 30 minutes daily 3 years post-HTx, HRQoL scores were high and comparable to those in the age- and sex-adjusted general population. The clinical implications of this study are that early supervised cardiac rehabilitation seems to have sustainable effects on the daily PA after HTx. However, only a few participants continued with HIT after the supervised intervention. Future research should focus on the effects of different HIT protocols (shorter exercise bouts) that might be easier to continue in the long term after HTx.

ACKNOWLEDGMENTS

We extend our thanks to all the HTx recipients who contributed to the HITTS trial. We also wish to thank Simon Fougner Hartmann's Family foundation for funding a new bio-impedance analyzer.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*. This project is funded through a PhD grant from the Norwegian Health Association and a postdoctoral grant from the South-Eastern Norway Regional Health Authority.

DATA AVAILABILITY STATEMENT

Research data are not shared due to Norway's strict regulations regarding privacy and data protection.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Rolid K, Andreassen AK, Yardley M, et al. Long-term effects of high-intensity training vs moderate intensity training in heart transplant recipients: A 3-year follow-up study of the randomized-controlled HITS study. *Am J Transplant*. 2020;20:3538-3549. <https://doi.org/10.1111/ajt.16087>

Supplementary Table 1. Demographic characteristics and exercise capacity from the HITTS-study, the SCHEDULE (SCandinavian HEart transplant everolimus De-novo stUdy with earLy calcineurin inhibitors avoidancE)-trial -3-year results¹ and historical data from Oslo University Hospital, Rikshospitalet²

	HITTS study-3 year follow-up (n= 62)	SCHEDULE 3-year follow-up¹ (n=49)	Older data from Oslo University Hospital, Rikshospitalet² (n=174)
Sex (% men)	76	74	87
Age (years)	52 ± 13	49 ±14*	51 ± 0.9
Time after HTx (years)	3	3	3.5 ± 0.2
VO_{2peak} (mL/kg/min)	24.1 ± 7.6	24.2 ± 7.1**	19.4 ± 0.4**

Data are expressed as mean ± SD or percentages

*Baseline data 7-11 weeks after HTx **Bicycle test (VO₂ values are usually 5-10% lower than performed on a treadmill)

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