Chronotropic responses and effect of high intensity interval based aerobic exercise in heart transplant recipients

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What this thesis is about

Several factors might explain the reduced exercise capacity observed in heart transplant (HTx) recipients of which the most obvious is chronotropic insufficiency due to denervation of the heart. Our main hypotheses, however, were that chronotropic incompetence would not be a limiting factor in performing high intensity interval training (HIIT) and that HIIT would improve peak oxygen uptake ($\text{VO}_{2\text{peak}}$) in HTx recipients in a stable phase. Secondly, we wanted to evaluate factors associated with a high versus low $\text{VO}_{2\text{peak}}$ level, and the effect of HIIT on cardiac allograft vasculopathy (CAV). We also aimed to investigate possible mechanisms behind a potential increase in $\text{VO}_{2\text{peak}}$, evaluating both central and peripheral factors, using several methods such as: isokinetic muscle strength testing; newer echocardiographic assessment; 24 hours Holter monitoring; measurement of body composition; measurement of systemic inflammation and health related quality of life (HRQoL).

The first article included in this thesis was based on a prospective, observational study investigating the improvement in chronotropic responses the first year following a HTx (n=77). The remaining articles in this thesis were based on our main study, which was a randomized controlled trial, primarily investigating the effects of a one year HIIT intervention in stable, long-term HTx recipients (n=52).

Our main goal was to demonstrate that the exercise restrictions that traditionally have applied to a transplanted, denervated heart may be disregarded, and to dispose of the belief that HIIT is unphysiological and unsuitable in HTx recipients. On the contrary, it can be a safe and efficient form of exercise resulting not only in increased $\text{VO}_{2\text{peak}}$, but also in an over-all increased health.

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Abbreviations

BMI	body mass index
BPM	beats per minute
CAD	coronary artery disease
CAV	cardiac allograft vasculopathy
CRI	chronotropic response index
HIIT	high intensity interval training
HR	heart rate
HRQoL	health related quality of life
HRV	heart rate variability
HTx	heart transplant
IL	interleukin
IVUS	intra vascular ultra sound
LV	left ventricle
MIT	maximal intima thickness
PAV	percent atheroma volume
RCT	randomized controlled trial
RER	respiratory exchange ratio
RPE	rated perceived exertion
TAV	total atheroma volume
VAS	visual analogue scale
VH	virtual histology
VO _{2peak}	peak oxygen uptake

List of Publications

- Paper I** Nytrøen K, Myers J, Chan KN, Geiran OR, Gullestad L. Chronotropic Responses to Exercise in Heart Transplant Recipients: 1-Yr Follow-Up. *Am J Phys Med Rehabil* 2011;90(7):579-88, DOI: 10.1111/j.1600-6143.2012.04221.x
- Paper II** Nytrøen K, Rustad LA, Gude E, Hallén J, Fiane AE, Rolid K, Holm I, Aakhus S, Gullestad L. Muscular exercise capacity and body fat predict VO₂peak in heart transplant recipients. *Eur J Prev Cardiol* 2012 June 1 [E-pub ahead of print], DOI: 10.1177/2047487312450540.
- Paper III** Nytrøen K, Rustad LA, Aukrust P, Ueland T, Hallén J, Holm I, Rolid K, Lekva T, Fiane AE, Amlie JP, Aakhus S, Gullestad L. High-Intensity Interval Training Improves Peak Oxygen Uptake and Muscular Exercise Capacity in Heart Transplant Recipients. *Am J Transplant* 2012;12(11):3134-3142, DOI: 10.1111/j.1600-6143.2012.04221.x
- Paper IV** Nytrøen K, Rustad LA, Erikstad I, Aukrust P, Ueland T, Gude E, Lekva T, Wilhelmsen N, Hervold A, Aakhus S, Gullestad L, Arora S. Effect of high-intensity interval training on progression of cardiac allograft vasculopathy. *J Heart Lung Transplant* 2013;32:1073-1080, DOI: 10.1016/j.healun.2013.06.023

1. Introduction

Heart transplantation (HTx) gives numerous patients with end-stage heart disease a second chance of life. However, although life expectancy is greatly improved, survival is reduced mainly due to increased frequency of late complications, and exercise capacity and health related quality of life (HRQoL) is reduced compared with the general population (1). The exercise capacity improves after a heart transplant compared with end-stage heart failure (2-8), but it continues to be subnormal compared with age-matched values in normal individuals. The peak oxygen uptake (VO_{2peak}) levels range from 50% to 70% of predicted in most studies (Table 1), and a reduced VO_{2peak} level is generally associated with a poorer prognosis (9). Only a few reports exist on individuals reaching close to normal VO_{2peak} levels (10;11). Both central hemodynamics and peripheral physiological abnormalities may explain the reduced exercise capacity (Table 2). Among factors considered are reduced cardiac output due to chronotropic incompetence or reduced stroke volume, peripheral abnormalities including reduced muscle strength and oxidative capacity or abnormal blood supply due to impaired vasodilatory capacity or capillary density (12).

Several studies demonstrate an effect of aerobic exercise after HTx, but almost all have used a protocol consisting of moderate training (Table 3). Traditionally, mainly due to chronotropic incompetence because of denervation, HTx recipients have not been exposed to interval-based exercise with higher intensity because it has been considered “unphysiological”. Such exercise; high intensity interval training (HIIT), has repeatedly proven to be a highly efficient form of exercise to improve physical capacity in normal subjects as well as in patients with coronary artery disease (CAD) and heart failure (13-15). With differences in various patient groups, HIIT has demonstrated improvement in both central and peripheral factors such as stroke volume, left ventricle (LV) remodeling, blood volume and flow, blood pressure, endothelial function, biochemical markers, skeletal muscle

function and HRQoL (14-16). However, except for a few small studies introducing high intensity exercise to HTx recipients (11;16), the effects of a long-term HIIT intervention have, to our knowledge, not been investigated.

Table 1 Summary of observational studies describing $\text{VO}_{2\text{peak}}$ levels in heart transplant recipients

Study	<i>N</i>	Mean age (years)	Mean time after HTx (years or months)	$\text{VO}_{2\text{peak}}$: mL/kg/min or L/min	$\text{VO}_{2\text{peak}}$ (% of age-predicted value)	Percent of age-predicted HR_{max} or actual HR_{max} (bpm)	Type of study
Ulubay et al. 2007 (17)	7	43 ± 14	19 months	1.45 ± 0.33 (L)	NA	114 ± 41 (bpm)	Observational
Carter et al. 2006 (2)	47	48	5 years	16.1 ± 0.5 (mL)	51 ± 1.5 (%)	74 ± 1 (%)	Observational
Richard et al 2005 (18)	7	40 ± 13	2 years	NA	101 ± 12 (%)	93 ± 9 (%)	Observational
Semid et al. 2005 (19)	17	58 ± 13	65 ± 27	20.9 ± 5.2 (mL)	NA	136 ± 12 (bpm)	Observational
Myers et al. 2003 (20)	47	47 ± 12	4.8 years	9.4 ± 2.6 (mL)	59 ± 14 (%)	129 ± 18 (bpm)	Observational
Gullestad et al 2003 (21)	174	51 ± 1	3.5 years	19.4 ± 0.4 (mL)	70 ± 1 (%)	146 ± 2 (bpm)	Observational
Squires et al. 2002 (22)	95	48 ± 14	1 year	19.9 ± 4.8	61 ± 15 (%)	138 ± 22 (bpm)	Observational
Douard et al. 1997 (23)	85	52 ± 12	0-100 months	21.1 ± 6 (mL)	NA	85 ± 13 (%)	Observational
Notarius et al. 1997 (12)	12	51 ± 4	8 months	17.3 ± 1.7 (mL)	57 (%)	147 ± 7 (bpm)	Observational
Osada et al. 1997 (24)	56	50 ± 12	3 years	20.0 ± 5.0 (mL)	70 ± 17 (%)	88 ± 11 (%)	Observational
Mandak et al 1995 (25)	60	52 ± 10	1 year	16.2 ± 3.8 (mL)	NA	137 ± 24 (bpm)	Observational
Renlund et al. 1995 (26)	110	51 ± 10	26 months	17.7 ± 0.3 (mL)	64 ± 1 (%)	85 (%)	Observational

HTx, heart transplant; HR_{max} , maximum achieved heart rate; bpm, beats per minute; NA, value not available.

1.1 The transplanted, denervated heart

In contrast to the normal heart's chronotropic response to exercise, a newly transplanted heart is denervated, which causes higher resting heart rate (HR) and chronotropic incompetence (8). The HR response during exercise is mainly controlled by catecholamines from the adrenal glands, resulting in a significantly slower increase of the HR at onset of exercise, a reduced peak HR, and a delayed return towards resting values after stopped exercise (4;8;27;28). It is a common belief that this slow HR is of great importance when designing rehabilitation programs early after HTx, especially the very first year. We have demonstrated an improved HR response to exercise the first year after surgery (Paper I), but the mechanisms behind; if they are due to a reinnervation, and what the importance of a possible reinnervation is, remain unclear (22;29;30). Existing studies have yet no unambiguous answers to this question.

1.2 Exercising with a transplanted heart

Knowledge about the denervated heart is important in order to adjust for optimal effect of physical exercise. There are now several, but small, studies which show that aerobic exercise gives a higher exercise capacity in HTx recipients (3;5;6;31-34). The exercise has mainly consisted of steady-state¹ training, with moderate intensity, which has positive effects (3;5;6;32-34), but the increase in exercise capacity and the VO_{2peak} levels reached are moderate (3;5;6;32-34).

There are much evidence and research present when it comes to effect of rehabilitation and exercise in non-transplant patients in general (35). At present, accumulating evidence suggests that high intensity aerobic training, and especially interval based training, is a favorable type of exercise, with improvement of both peripheral and central factors

¹ Steady State training means no rapid changes in intensity. It is exercising with an even heart rate.

(13;14;36). Wisløff et al. (14) have shown that interval training improved VO_{2peak} with 46% in patients with heart failure, but whether this type of exercise is suitable for HTx patients has been unclear.

It is assumed that the delayed HR response after HTx is a limitation when it comes to adapting to interval training. Newly HTx patients are, because of their slow HR response, in need of a thorough warm-up period, which should be followed by steady state¹ aerobic exercise. Although the HR response to exercise improves with time after HTx, the prevailing opinion is that these patients should not participate in interval training. This considerably limits their possibilities to join existing rehabilitation programs in their home environment, and whether this form of exercise really is unsuitable for this group of patients or not, has not yet been thoroughly investigated.

1.3 Effect of exercise in heart transplant recipients

The first randomized controlled trial (RCT) investigating the effect of exercise in HTx recipients was published in 1999 by Kobashigawa et al. (3). The trial included patients one month post HTx and compared a six-months rehabilitation program to a control group receiving no specific exercise strategy. The mean change between the groups at follow-up was 3.4 mL/kg/min ($p<0.001$), but the VO_{2peak} level reached at the end of the intervention was low compared to age and sex predicted values in healthy subjects. This is also reflected in most of the following trials. Table 3 describes the details of the published RCTs in the period from 1999 to 2011. The mean VO_{2peak} values reached after the exercise interventions range from 13.2 to 28.3 mL/kg/min in the various studies, and the mean change between the control and exercise groups ranges from 1.3 to 5.6 mL/kg/min.

Except from the most recent study by Herman et al. (16), which was published two years after the start-up of the current PhD project, the mean intensity of the aerobic training was reported to be 60-80% of VO_{2peak} in most studies, the exercise duration ranged from 30 min to 1,5 hours, 2-5 times per week for 8 weeks up to 1 year, the mean time after HTx ranged from 1 month up to 7 years, and the number of participants ranged from 24 to 43 (Table 3).

Based on the great differences between these trials and the inconsistent results, one can only conclude that exercise improve VO_{2peak} , but it is not possible to state which type of exercise, intensity and duration that give optimal results.

Table 2 Possible mechanisms associated with reduced exercise capacity in HTx recipients

I Central Cardiac Factors

- Reduced cardiac output
 - chronotropic incompetence
 - Reduced stroke volume
 - Systolic dysfunction
 - Diastolic dysfunction
- Pulmonary dysfunction
 - Pulmonary hypertension
 - Lung disease
 - Pulmonary congestion

II Peripheral Factors

- Decreased skeletal muscle function
 - Reduced muscle mass
 - reduced muscle strength
 - reduced capillary density
 - reduced oxidative capacity
 - reduced mitochondrial function
 - corticosteroid induced myopathy
 - Impaired vasodilatory capacity
 - Endothelial dysfunction
 - Deconditioning
-

Other potential factors contributing to reduced exercise capacity

- increasing age
- donor age
- donor match
- ischemic time
- pre transplant de-conditioning
- primary diagnosis
- co-morbidities
- smoking
- cultural differences
- gender differences
- anxiety and depression
- socio-economic status
- reduced HRQoL

Table 3 Summary of RCTs investigating effect of exercise in HTx recipients

Study	n / mean age (years)	Mean time after HTx	Intervention	Mean change in $\dot{V}O_{2peak}$ (mL/kg/min) within groups	Mean change in $\dot{V}O_{2peak}$ (mL/kg/min) between groups
Kobashigawa et al. 1999 (3)	N=27, age 52	1 month	6 months partly supervised rehabilitation program vs. controls <i>Walking, cycling and upper- and lower limb exercises for 30 min 1-3/week.</i>	Ex: 9.2 → 13.6 Con: 10.4 → 12.3	2.5
Tegtbur et al. 2005 (32)	N=32, age 55	5 years	1 year home based exercise program vs. controls <i>Cycling every other day for 1 year at 80-90% of maximum HR.</i>	Ex: 18.6 → 20.0 Con: 18.9 → 19.0	1.3
Bernardi et al. 2007 (6)	N= 24, age 52	6 months	6 months home training vs. controls <i>Cycling at 60-70% of $\dot{V}O_{2peak}$ 30 min x 5/week x 6 months</i>	Ex: 14.9 → 19.6 Con: 14.3 → 15.6	3.4
Karapolat et al. 2008 (5)	N= 28, age 42	1.5 years	8 weeks supervised hospital training vs. home based training <i>1.5 hrs of multiple exercises including aerobic exercise for 30 min at 60-70% of $\dot{V}O_{2peak}$ x 3/week. Controls received written guidelines on exercises and a walking program.</i>	Ex: 16.7 → 19.5 Con: 20.1 → 19.5	3.4
Wu et al. 2008 (33)	N= 37, age 56	2 years	8 weeks home training vs. controls <i>Strength training and aerobic exercise at 60-70% of $\dot{V}O_{2peak}$, 35-40 min 3/week.</i>	Ex: 12.1 → 13.2 Con: 13.7 → 13.2	1.6
Haykowsky et al. 2009 (31)	N= 43, age 59	5 years	12 weeks aerobic & strength training vs. controls <i>First 8 weeks: continuous aerobic exercise at 60-80% of $\dot{V}O_{2peak}$ 30-45 min x 2/week. Continuous aerobic training at 80% of $\dot{V}O_{2peak}$, 45 min x 2/week and bicycle interval training for 30 s at 90-100% of $\dot{V}O_{2peak}$ followed by 60 s rest for 10-25 reps x 2/week in the final 4 weeks. Resistance training at 50% of 1RM, 10-15 reps x 1-2 sets x 4 exercises x 2/week for 12 weeks</i>	Ex: 21.2 → 24.7 Con: 18.2 → 18.2	3.5
Hermann et al. 2011 (16)	N= 27, age 50	7 years	8 weeks high intensity interval training vs. controls <i>Interval blocks of 4 min/2 min/30 s according to 80%, 85% and 90% of $\dot{V}O_{2peak}$, and recovery periods of 1/2 min, and finally staircase running at 80% of $\dot{V}O_{2peak}$ followed by recovery walking, 60 min x 3/week.</i>	Ex: 23.9 → 28.3 Con: 24.6 → 23.4	5.6

RCT, randomized controlled trial, HTx, heart transplant; Ex, exercise group; Con, control group; 1RM, 1 repetition maximum; HR, heart rate

1.4 Mechanisms of reduced exercise capacity among heart transplant recipients

Both central hemodynamic and peripheral physiological factors probably contribute to the reduced exercise capacity in HTx recipients (Table 2). Among central factors considered are chronotropic incompetence, impaired LV function or greater arteriovenous oxygen difference, while peripheral limitations could include reduced muscle mass, anabolic resistance due to reduced muscle strength and oxidative capacity, or abnormal blood supply due to impaired vasodilatory capacity and capillary density. Several factors specific for HTx patients, such as the immunosuppressive regimen, donor age, and ischemic time, as well as general factors such as smoking status, prolonged de-conditioning, co-morbidities, socio-economic status, and cultural differences may contribute to the reduced performance (7;12;23;28;37;38) (Table 2).

1.5 Reinnervation

“Total denervation persists in the human heart following cardiac transplantation” was in 1992 stated in an article by Shephard (39), and it was the common belief in most research communities in early studies among HTx recipients. Accumulating evidence of the opposite has the last decade repudiated this statement. Techniques such as analyses of heart rate variability (HRV), baroreflex stimulation, scintigraphy (single-photon emission computed tomography [SPECT] and positron emission tomography [PET]) have provided well established evidence of sympathetic reinnervation (40-42). Signs of parasympathetic reinnervation are also described (43-45), although it seems to be more uncertain. Furthermore, normalization of the chronotropic responses is associated with functional reinnervation and a better exercise capacity (6;23;40-42;46;47).

1.6 Health related quality of life

Studies investigating HRQoL after HTx have evidently showed that HTx recipients significantly improve their HRQoL compared to the pre transplant stage (48-53). These studies have mainly used generic questionnaires or a combination of generic and disease specific questionnaires (48-53). Several studies report that the improved HRQoL also remains high long-term after HTx (48;49;54-57), while we have found reduced HRQoL among HTx patients long term after surgery compared with newly transplanted patients (49).

Compared with HRQoL scores in general populations, HTx populations demonstrate various results. Some studies report no HRQoL differences between HTx recipients and a general population (52;56;57), whereas we and others have reported that HTx populations have significantly lower HRQoL scores compared with a reference population (49;54;55;58-62). Furthermore, reduced HRQoL is associated with anxiety and depression after HTx (51;53;60;63).

1.7 Cardiac Allograft Vasculopathy – general aspects

Cardiac allograft vasculopathy (CAV) (figure 1) is a rapidly progressive form of atherosclerosis occurring in HTx recipients involving diffuse thickening and occlusion of the coronary arteries (64). The classic early sign of CAV; intimal thickening, is present in about 58% of the arteries during the first year after HTx (65;66). Later, luminal stenosis of the epicardial branches and occlusion of smaller arteries develop, secondarily resulting in myocardial ischemia and infarction (67). CAV is a great therapeutic challenge, and it is the leading cause of late graft loss and death among HTx patients. The only real cure for severe CAV is retransplantation (64;67).

Because of denervation myocardial ischemia may be asymptomatic, and in many cases CAV can only be diagnosed by coronary angiography or intravascular ultra sound (IVUS).

IVUS increases the sensitivity for early diagnosis compared to traditional angiography (64)

(Figure 2).

Figure 1 **Typical atherosclerosis versus cardiac allograft vasculopathy (CAV).** Focal lesions characterize typical atherosclerosis, while diffuse intimal thickening characterize CAV.

(The image is reproduced with permission from NEJM (2003), © Massachusetts Medical Society)

Figure 2
Diffuse intimal thickening can be accurately identified by IVUS in contrast to angiography where only the lumen size is visible.

Existing therapy options treating CAV, including anti-proliferative drugs, everolimus and sirolimus as well as statin therapy early after HTx, has so far not given the desired results (67-69). In clinical practice, prophylaxis of CAV involves modification of general risk factors such as smoking, obesity, diabetes and hypertension as well as implementation of physical activity (70). However, although the atheroprotective effect of exercise and the effect of physical activity on established coronary artery disease is well established (71;72), with a more pronounced effect of HIIT (14;73), the specific effect of exercise on CAV, has to our knowledge, not yet been reported.

1.8 High intensity interval training

American College of Sports Medicine (74) and American Heart Association's (75) recommendation for exercise, is to exercise with an intensity between 50% and 90% of maximum VO_2 , which refers to approximately 60% to 95% of the maximum HR. Compared to detailed prescription of different medications, this is a very inaccurate recommendation, which is difficult both for health personnel obligated to give advice based on these recommendations, and practically for the patients, in order to carry out these vague exercise prescriptions. One of the reasons for the imprecise recommendations is that there through

decades have been uncertainty and disagreement regarding how $\text{VO}_{2\text{peak}}$ improves most efficiently. The majority of researchers in the field now agree that the major factor limiting an individual's $\text{VO}_{2\text{peak}}$ is the stroke volume. Given that maximum HR cannot be increased, the stroke volume is the limiting factor, and the only factor, that through exercise may improve cardiac output (76). It is reasonable to think that exercise at a near to maximum stroke volume would give the best results. The previous belief was that maximum stroke volume was reached around 50% to 70% of maximum HR (73;77), and this is still stated in most textbooks (76) although it was shown as early as in the 1960's that the stroke volume not necessarily did plateau (78). Additional and more recent research have documented, both in untrained, moderate and well trained subjects, that the stroke volume often doesn't reach a plateau until the HR reaches close to it's maximum (79-83). This is not documented in patients with CAD, but several studies with high intensity exercise interventions have documented superior effect of such exercise compared to exercise at a moderate intensity, both in patients with heart failure and CAD (13;14;84-86).

Most individuals should be able to reach an intensity of approximately 90% to 95% of their maximum HR within 1-2 minutes. Based on this, the leading research community of this field in Norway (Norwegian University of Science and Technology, Trondheim), have proposed, and well documented, that 4 exercise bouts of 4 minutes each (4 x 4), with an active break in between (Illustrated in figure 4), is an exercise prescription that is highly effective and applicable also for patients with CAD (73).

2. Main Aims of the Thesis

- 1.** To evaluate alterations in chronotropic responses to exercise during the first year after heart transplantation and to estimate the probability / odds for developing normalization of chronotropic responses within one year after heart transplantation.
- 2.** To evaluate the exercise capacity in a group of heart transplant recipients, and investigate central and peripheral factors determining their $\text{VO}_{2\text{peak}}$ level.
- 3.** To evaluate the effect of HIIT on exercise capacity and to evaluate possible central and peripheral effects of such training in stable, long-term heart transplant recipients.
- 4.** To evaluate whether HIIT could attenuate the development of cardiac allograft vasculopathy in stable, long-term heart transplant recipients.

3. Subjects and Methods

Oslo University Hospital Rikshospitalet is the only transplantation center in Norway and all the HTx patients included in the studies are recruited from our center.

3.1 Study No.1; Pre Study

This was a prospective, observational study aiming to document alterations in HR response during rest, exercise and recovery period throughout the first year after a HTx, and to estimate the probability / odds for developing normalization of chronotropic responses within one year following HTx. During the period from 2002-2007, 179 patients underwent HTx at our center, of which 146 were referred to an in-hospital exercise program. Seventy-seven of these patients were included in this observational study after meeting the following criteria: all remained clinically stable, were able to exercise, and had performed at least two of the three planned exercise tests throughout the first year after HTx. The study population is further described in Paper I. The study was approved by the Department of Privacy and Data Security in our hospital.

3.1.1 Measurements

Exercise test

The exercise test was performed approximately at 1, 6 and 12 months after HTx and consisted of a 10 min resting period in the supine position, a 5 min warm-up period with cycling at a low constant load (women 35 watts and men 50 watts), immediately followed by climbing stairs at maximum effort for 2.5 minutes (rated perceived exertion (Borg 6-20 scale) > 18 (87), and finally a recovery period of 10 min in the supine position. The HR was continuously recorded during exercise with a Polar HR monitor (Polar Accurex Plus / Polar S810i, Polar

Electro Oy, Finland), and the HR data were analyzed using the Polar Precision Software version 4.03.049 (Polar Electro Oy, Finland).

Definition of chronotropic variables

Resting HR is the lowest measured HR during the initial resting period with a value > 90 considered pathological (88).

HR increase was defined as time (measured in seconds) from initiation of exercise (rising up from the supine position) until an increase of at least two beats per minute (bpm) occurred, under the condition that the HR continued to rise beyond the two bpm.

HR decrease was defined as time (measured in seconds) from the moment the exercise stopped and the patient was back in the supine position until a decrease of at least two bpm took place, under the condition that the HR continued to fall beyond the two bpm.

HR recovery (HRR), a more commonly used measurement for HR decrease, was measured by the reduction in HR after 1 and 2 min (HRR_1 and HRR_2), with values less than 12 and 22 bpm, respectively, considered abnormal (89;90).

HR peak was the peak HR during exercise. A value less than 85 % of age-predicted HR max (% *HR max*; percentage of $220 - \text{age}$) was considered abnormal (89;91;92).

HR reserve was measured by the difference between HR peak and HR rest, and age-predicted HR reserve (% *HR reserve*), often described as *the Chronotropic Response Index (CRI)* was calculated as: $[\text{HR peak} - \text{HR rest} / 220 - \text{age} - \text{HR rest}]$, where a ratio of less than 0.8 was considered abnormal (5;89).

3.2 Study No. 2; Main Study

This was a RCT investigating the effect of a one-year HIIT intervention in HTx recipients.

We prospectively recruited 57 clinically stable HTx patients from a cohort of 231 potential

participants during their annual follow-up between 2009 and 2010. The major reasons for not being recruited were resources to include only two patients per week and/or not meeting the inclusion criteria. Of the 57 patients, five were excluded for the following reasons: withdrawal (1) and logistics (4), (Figure 1 in Paper III).

Fifty-two patients underwent baseline testing and were randomized, using computer generated randomization sequences. Consecutively numbered, sealed envelopes were provided by an independent statistician before inclusion started and the participants were randomly assigned in a 1:1 ratio to either intervention group (HIIT) or control group (usual care), stratified by time after heart transplant surgery (1-2 years after HTx and 3-8 years after HTx).

Paper II and Paper III have a detailed description of the study population. Paper II is based on baseline data only (n=51), and Paper III describes differences between the groups at one year follow-up (n=48). Paper IV was planned as a sub-study, in parallel with the main study, especially investigating the effect of HIIT on CAV (n=43).

The study was approved by the South-East Regional Ethics Committee in Norway and by the Department of Privacy and Data Security in our hospital. All procedures were performed in accordance with the recommendations in the Helsinki Declaration. ClinicalTrial.gov identifier: NCT 01091194.

3.2.1 Exercise intervention

The exercise intervention was HIIT performed on a treadmill. Twenty-four patients from 24 different geographical communities throughout Norway completed the HIIT program, which lasted for one year (Figure 3). The exercise intervention was carried out de-centralized; each patient was assigned to a local, cooperating physical therapist for individual supervision of every single HIIT session. The year was divided into three 8-week periods of exercise with

three sessions every week; a total of 72 HIT sessions during one year. Both during and after each 8-week period, we were in close contact by mail and/or phone with the patient and the local physical therapist in order to discuss progression and compliance. Compliance was measured as number of completed HIIT sessions throughout the year. In between the supervised 8-week periods, the patients were encouraged to continue physical activity on their own. All participants were provided with their own heart rate monitor (Polar FT1, Polar Electro Oy, Finland) and both the supervised sessions and their solo training were carefully monitored and logged in order to document level of intensity, duration and frequency throughout the intervention period. During the supervised sessions the physical therapist noted the HR on a pre-specified sheet towards the end of each 4 min exercise bout, and after each solo training session the participant collected and noted saved data from the HR monitor: total exercise time, mean and maximum HR during the exercise session.

The HIIT sessions were carried out using the 4 x 4 method (73) consisting of a 10 min warm-up period followed by four 4 min exercise bouts at 85-95% of maximum heart rate (HR_{max}), interposed by 3 min active recovery periods (Figure 4), corresponding to approximately 11-13 on the Borg rated perceived exertion (RPE) scale. HR_{max} recorded during the baseline, maximal exercise test was used to determine each patient's training zone. During the year of exercise, the patients' HR_{max} was repeatedly assessed and training zones adjusted if necessary, and each 8-week period was evaluated in co-operation with the local physical therapist.

The control group underwent the same test protocols as the HIT group, at baseline and after 12 months, but no special intervention was given in between other than basic, general care given to all HTx patients.

Figure 3 The exercise intervention

Figure 4 Example of a 4 x 4 HIIT session performed by one of the patients, demonstrating the distinct rise and fall of the HR between the high intensity 4 min exercise bouts and the active rest periods.

3.2.2 Measurements

Cardiopulmonary exercise test / treadmill protocol

We used a modified test protocol from the Working Group on Cardiac Rehabilitation and Exercise Physiology and Working Group on Heart Failure of the European Society of Cardiology (93). Patients started with a warm up of 10 min on a Runrace Treadmill (Technogym, Cesena, Italy), during which their individual walking speed (3-6 km/h) was determined. After the 10 min warm-up, the inclination of the treadmill was increased by 2% every 2 min until exhaustion. Test termination were symptom limited and none of the tests were terminated until a respiratory exchange ratio (RER) >1.05 and/or rated perceived exertion (Borg 6-20 scale) > 18 (87). Lung function and breath-by-breath gas exchange were measured using the Sensormedics Vmax (Yorba Linda, CA, USA). ECG and HR were monitored continuously before, during and after exercise. The O_2 uptake, CO_2 production, O_2 pulse (mL/min), maximum ventilation (VE_{max}), ventilatory efficiency (VE/VCO_2 slope) and RER were calculated online. Anaerobic threshold (ventilatory threshold) was also calculated online using the V-slope method (94). Blood pressure was measured automatically (Tango, Sun Tech Medical Instruments, NC, USA) before exercise, every 2 min during exercise and after exercise. After test termination, the patients rested in an upright position for a 2 min recovery period. VO_{2peak} was calculated as the mean of the three highest 10 second measurements at peak exercise. HR_{peak} was the peak HR during exercise and age-predicted maximum HR and CRI were calculated as described above (Study No 1).

Muscle strength and muscular exercise capacity

Quadriceps and hamstrings muscle strength were tested isokinetically on a Cybex 6000 (Lumex, Ronkonkoma, NY, USA). The patients were in a sitting position, testing one leg at a time. Muscle maximal strength was tested at an angular velocity of $60^\circ/s$. Five repetitions

were performed, with the mean peak value in Newton meters (Nm) calculated for each patient. Muscular exercise capacity was measured as total work during 30 isokinetic contractions at 240°/s, with total work in Joule (J) calculated as the sum of all repetitions.

Bioelectrical impedance analysis

Bioelectrical impedance analysis (BIA) is considered a reliable and more accessible method of body composition screening than dual-emission X-ray absorptiometry (DXA) (95). Our body composition data were collected using the Tanita 418MA and BC-558 systems (Tanita, Arlington Heights, IL, USA). All patients were screened at the same time of the day with means of three measurements calculated for all patients. The recorded variables included body mass index (BMI), amount of body fat, total body water, muscle mass, visceral fat, bone mass, metabolic age and basal metabolic rate.

24 hours Holter monitoring and heart rate variability analysis

Heart rate variability (HRV) is a marker of autonomic activity and was recorded using a 3-channel Medilog Holter FD3 monitor (Schiller, Baar, Switzerland). The recordings were analyzed using the corresponding Medilog software version 4.2. All the recordings were edited by an experienced technician before analysis. HRV describe variations of both instantaneous HR and RR interval and were evaluated by both time and frequency domain method (96). The high frequency (HF) component mirrors only vagal activity, while the low frequency (LF) component usually reflects both sympathetic and vagal activity. The LF/HF ratio is by many considered to reflect symtovagal balance. The time domain variables also have approximate frequency domain correlates (96).

At follow-up we had a low number of matched Holter recordings ($n=34$) as a result of a non-intentional deletion of all the recordings from 2009, and also several excluded unpaired

recordings, because of missing baseline or follow-up recording. In addition, a few recordings were excluded from analysis because of a too large amount of missing data or noise, and some of the recordings were difficult to analyze because of borderline too much noise. Therefore, these data are only cautiously mentioned and not shown in any of the published articles.

Health Related Quality of Life and Symptoms of Anxiety and Depression

HRQoL was measured with the generic questionnaire Short Form 36, version 2 standard form (SF-36v2) (97) and the disease-specific questionnaire Kansas City Cardiomyopathy Questionnaire (KCCQ) (98;99). The SF-36 contains 36 items that measure HRQoL on eight scales (Table 4), which were aggregated into two sum-scores: Physical Component Summary (PCS) and Mental Component Summary (MCS). The eight scales and the two summary scores were reported on a standardized scale with a mean of 50 and a SD of 10, based on the 1998 United States general population. The KCCQ contains 23 items that measure HRQoL on six scales, which were aggregated into two sum-scores; Clinical sum-score and Functional Status sum-score. The scales and the two sum-scores were reported on a 0-100 scale, higher scores representing better HRQoL (98;99). In addition to the two HRQoL questionnaires, patients were asked to subjectively rate on a visual analogue scale (VAS) how much participation in this study had improved their general health and HRQoL; “0” indicating nothing and “100” indicating extremely much. Symptoms of depression and anxiety were measured with the Hospital Anxiety and Depression Scale (HADS) (100) and Beck Depression Inventory (BDI) (101). HADS-A and HADS-D sum-score less than 8 indicates no symptoms of anxiety and depression, respectively. BDI sum-score less than 10 indicates no symptoms of depression.

Echocardiography

A standard echocardiographic examination was performed with GE Vivid 7 or E9 (GE Vingmed Ultrasound, Horten Norway), with the participants in the left lateral position. The data were stored digitally and analyzed off-line with dedicated software (EchoPac, GE Vingmed Ultrasound, Horten, Norway). Three consecutive heart cycles were obtained from three apical projections; images with two-dimensional grey-scale echocardiography and color tissue Doppler imaging (cTDI). LV ejection fraction (EF) and LV volumes were measured with the modified Simpson method, using the four- and two-chamber views (102;103). LV mitral annular velocities in early diastole (LVe') were averaged from cTDI measurements at the septal, lateral, anterior and posterior points (103;104).

Exercise echocardiography was performed on a bicycle ergometer (Ergoline, Germany), with the patients in a semi-supine position, pedaling at 50-65 rounds per minute, starting with a workload of 25 watt (W), with an increase of 25 W every 2 minutes. Images were obtained at rest, at 50 W, 100 W and at sub-maximal level, defined by incipient muscular fatigue (103).

Biochemistry

Regular blood screening was performed in the morning, in fasting site for all patients; hemoglobin (Hb), white blood cells, C-reactive protein (CRP), creatinine, urea, estimated glomerular filtration rate (eGFR), uric acid, liver and thyroid function, lipid status, glycaemic control and N-terminal prohormone of brain natriuretic peptide (NT-proBNP). From 18-mL samples, 6 mL was used to prepare serum and 12 mL was used to prepare plasma. The plasma samples in EDTA (ethylene-diamine-tetra-acetic acid) -tubes were immediately placed on ice and centrifuged within 30 min to obtain platelet-poor plasma. Samples for serum were kept at room temperature for 1-2 hours, centrifuged and then supernatant fractions were removed into

cryotubes and frozen at -80° for later analysis. When analyzing NT-proBNP and CRP, the samples were thawed at room temperature and assayed on a MODULAR platform (Roche Diagnostics, Basel, Switzerland) (105). Interleukin (IL)-6, IL-8 and IL-10 were analyzed by enzyme immunoassays from R&D Systems (Minneapolis, MN, USA).

Intra vascular ultra sound

A standard intra vascular ultra sound (IVUS) examination (106) was performed after routine angiography with the Volcano Eagle Eye Gold catheter (Volcano Corporation, Rancho, Cordova, CA, USA), and all recordings were performed with the same motorized pullback device (with a pull-back speed of 0.5 mm/second) with an image acquisition rate of 15 frames/second. The recordings were then analyzed with the software QIVUS version 1.1.11.0 (Medis Medical Imaging, Leiden, Netherlands) and Virtual Histology analyses were performed using the pcVH version 2.2 (Volcano Corporation or QIVUS version 2.1.11.0).

IVUS imaging was performed in the same artery at baseline and follow-up for each patient, preferably the left-anterior descending coronary artery (LAD), and the same segment length was analyzed at baseline and follow-up (Figure 5).

Figure 5 Matched site-by-site intra vascular ultra sound analysis (Left image: baseline. Right image: follow-up)

All the IVUS recordings were analyzed by a blinded, experienced technician, and controlled by another person. Following manual contour detection of the lumen and external elastic membrane (EEM), lumen, vessel and intimal cross-sectional area (CSA) were calculated for all patients and utilized to determine total atheroma volume (TAV) and percent atheroma volume (PAV). Maximal intimal thickness (MIT) (Figure 2), defined as the greatest distance from the intimal leading edge to the external elastic membrane (EEM), was also calculated. At follow-up, we had 43 patients with matching segments.

Satisfactory virtual histology (VH) recordings were available in 38 patients. The contours were manually edited before the software constructed tissue maps with four major components: fibrous, fibrous fatty, dense calcified and necrotic core, of which all are expressed as a percentage of the total intima area.

3.3 Statistical analysis

Statistical analyses were performed with SPSS statistical software version 16.0 (Paper I) and version 18.0 (Paper II-IV) (SPSS Inc., Chicago, IL). Continuous data are expressed as mean $\pm$ standard deviation (SD), mean with 95% Confidence Interval (CI) or median with interquartile range.

Within-group comparisons were analyzed using paired *t*-tests (Paper III-IV) and one-way repeated Anova (Paper I) for normally distributed continuous variables, and Wilcoxon signed rank test for other continuous variables. Between-group comparisons were made using unpaired *t* or Mann–Whitney *U* tests where appropriate. For categorical data, χ^2 and Fischer's exact test were used. Bivariate relationships were explored in cross-tables and box- and scatter plots, with corresponding Pearson and Spearman correlation coefficients. To evaluate associations between dependent and independent variables, correlations, univariate and multiple regression (enter method) analyses were used. Model assumptions were thoroughly

checked for outliers, normality, homoscedasticity, independence of residuals, possible interactions and multi-co-linearity. Throughout the analyses, two-sided values of $p < 0.05$ were considered statistically significant.

3.4 Ethical considerations

The study described in Paper I was approved by the Department of Privacy and Data Security in our hospital, and the main, randomized study, described in Papers II-IV, was approved by the South-East Regional Ethics Committee in Norway and by our local Department of Privacy and Data Security. All procedures were conducted in accordance with the recommendations in the Helsinki Declaration. The main study was registered in the Clinical Trial Registration with the ID number NCT01091194, URL: <http://www.clinicaltrial.gov/ct2/show/NCT01091194>

All patients invited to join the study were in detail informed about the tests and the planned intervention. Because of the exercise restrictions that usually apply to a denervated heart, ethical issues about the safety and feasibility of a HIIT intervention were raised and discussed. These restrictions are mostly based on uncertainty and precautions rather than scientific evidence, and based on our own experience with these patients, the normalized chronotropic responses, accumulating evidence of reinnervation and documented efficacy of HIIT among patients with heart failure, we concluded that it would be more unethical *not* to offer this form of exercise to stable and healthy HTx recipients. Those who agreed to participate in this study gave their written informed consent and they were free to withdraw at any time point during the course of the study. The patients were thoroughly examined before entering the study and the inclusion criteria were carefully followed. There were no other ethical dilemmas in either of the studies.

4. Summary of Results

4.1 Paper I

Chronotropic Responses to Exercise in Heart Transplant Recipients – 1 Year Follow-Up

In this study, we investigated the improvements in chronotropic responses the first year following HTx.

Our main results were:

- At 12 months post HTx, 71% of the HTx recipients had achieved partial normalization of their HR response, defined as $HR_{max} > 85\%$ of predicted. The odds for normalization were 2.5 within the first year after HTx.
- The most significant changes took place within the first 6 months post HTx, with a further significant improvement towards 12 months.
- There were no changes in resting HR during the time of follow-up, whereas all other HR parameters improved during the study.
- The exercise capacity was significantly improved at 1 year, and improved exercise capacity was strongly associated with a higher HR peak and HR reserve.

4.2 Paper II

Muscular Exercise Capacity and Body Fat Predict VO_{2peak} in Heart Transplant

Recipients

In this study, we assessed different baseline characteristics and baseline values possibly associated with the VO_{2peak} levels among HTx patients 1-8 years after transplantation.

Our main results were:

- Chronotropic incompetence was not a limiting factor for exercise capacity in this study population.
- The most significant VO_{2peak} predictors in this study, representing only peripheral factors, were the amount of body fat and muscular exercise capacity.

4.3 Paper III

High Intensity Interval Training Improve Peak Oxygen Uptake and Muscular Exercise Capacity in Heart Transplant Recipients

In this study, we investigated the various effects of a one-year HIIT intervention in HTx recipients.

Our main results were:

- HIIT is a safe, applicable and efficient form of exercise in stable, long-term HTx recipients.
- HIIT significantly improved $\text{VO}_{2\text{peak}}$, muscular exercise capacity and general health in HTx recipients.
- HIIT resulted in a significantly lower heart rate and respiratory exchange ratio at sub-maximal exercise intensities (measured at 60% and 80% of peak exercise).
- HIIT did not improve left ventricular function as assessed by echocardiographic measurements.

4.4 Paper IV

High Intensity Interval Training Decrease Progression of Cardiac Allograft

Vasculopathy in Heart Transplant Recipients – Results From a Randomized Controlled Trial

In this sub-study, we investigated the effect of HIIT on CAV, in HTx recipients.

Our main result was:

- HIIT among maintenance HTx recipients resulted in a significantly impaired rate of CAV progression as assessed by IVUS.

4.5 Supplementary results

HRQoL results

At baseline the total study population had high HRQoL scores and no signs of depression or anxiety (Table 4). There were no significant improvements on any of the sum-scores or subscales of SF-36, KCCQ, HADS or BDI, possibly due to high baseline values and a ceiling effect, but there was a significant difference between the HIIT group and the control group on the SF-36 general health (GH) subscale, with a score of 54 ± 9 versus 49 ± 9 , respectively ($p < 0.05$) (Table 4). In general, the HIIT group had higher scores than the control group on all SF-36 scales and on the KCCQ clinical and functional sum-score, although not statistically significant. According subjectively improved health, the HIIT group reported 65 on the VAS scale versus 26 in the control group ($p < 0.001$) (Table 4). Neither of the groups had any symptoms of depression or anxiety at the time of follow-up.

24 h Holter recording / heart rate variability analysis

The 24 h Holter recordings ($n=34$) showed a significant reduction of minimum HR in the HIIT group and a trend towards higher values in the frequency domains total power (TP) and very low frequency (VLF). The other components of the frequency domain and the time domain were similar between the groups (data not shown).

Inflammation

As presented in figure six there were no significant differences between the groups in the measured inflammatory and anti-inflammatory biomarkers. Only the IL-8 level was significantly decreased within group (HIIT) at follow-up ($p < 0.05$).

Table 4: Health related quality of life and symptoms of depression and anxiety

	Exercise Group		Control Group		Mean difference between groups [95% CI]	<i>t</i> test <i>P</i>
	Baseline	Follow Up	Baseline	Follow Up		
SF-36						
MCS	52 ± 11	51 ± 14	54 ± 7	49 ± 12	3 [-6, 16]	0.468
PCS	50 ± 7	53 ± 7	50 ± 10	49 ± 10	3 [-3, 10]	0.317
Physical function (PF)	52 ± 4	53 ± 4	51 ± 7	50 ± 7	2 [-2, 6]	0.404
Role Physical (RP)	49 ± 8	52 ± 9	50 ± 10	46 ± 10	6 [-1, 14]	0.092
Bodily Pain (BP)	51 ± 10	52 ± 11	49 ± 11	49 ± 11	2 [-7, 10]	0.684
General health (GH)	51 ± 6	54 ± 9	53 ± 6	49 ± 9	7 [1, 13]	0.032
Vitality (VT)	54 ± 8	54 ± 11	52 ± 8	51 ± 11	2 [-5, 8]	0.645
Social function (SF)	50 ± 9	50 ± 12	52 ± 7	49 ± 10	3 [-5, 12]	0.419
Role emotional (RE)	50 ± 10	49 ± 12	51 ± 9	46 ± 13	4 [-4, 13]	0.311
Mental health (MH)	54 ± 9	53 ± 12	55 ± 7	51 ± 11	2 [-6, 10]	0.676
KCCQ						
Overall clinical sum-score	94 [91, 97]	96 [94, 97]	92 [89, 96]	90 [85, 95]	3 [-1, 8]	0.151
Functional status sum-score	94 [91, 97]	96 [94, 98]	93 [89, 97]	92 [88, 96]	3 [-1, 7]	0.170
VAS scale	-----	65 ± 27	-----	26 ± 26	39 [24, 54]	< 0.001
Anxiety and Depression						
HADS – anxiety sum-score	4 [3, 6]	6 [2, 10]	4 [3, 5]	5 [3, 7]	1 [-3, 5]	0.704
HADS – depression sum-score	2 [1, 4]	3 [1, 5]	3 [2, 4]	4 [2, 5]	-1 [-2, 1]	0.415
BDI sum-score	5 [3, 8]	6 [3, 9]	6 [4, 8]	7 [5, 9]	11 [-4, 2]	0.393

Data are expressed as mean ± SD or mean [95%CI].

SF-36, Short form with 36 items; MCS, mental component summary; PCS, physical component summary; KCCQ, Kansas city cardiomyopathy questionnaire;

VAS, visual analogue scale; HADS, hospital anxiety and depression scale; BDI, Beck's depression inventory

Figure 6 Mean changes between groups at follow-up in C-reactive protein (CRP), interleukin (IL) 6, 8 and 10. Error bars represent 95% Confidence Interval (CI).

5. General Discussion

The past few years there has been increasing focus on physical exercise as a tool in both primary and secondary prophylaxis of cardiovascular diseases, which is the main cause of sickness and death in the western world. Despite the increased focus and the great health benefits of exercise, it seems to be underutilized as a therapeutic intervention. In this project we intended to use an "up to date" physical training principle to a group of patients who not yet has been offered or accepted to this kind of exercise (HIIT). Traditionally, several exercise restrictions have applied to the denervated heart, which seems to be based more on carefulness than scientific evidence. Through this project, we wanted to obtain new knowledge about the effect of exercise, especially of HIIT, and possible mechanisms which could explain the effects. We hope that this knowledge will not only contribute to improve the heart transplants' life prognosis and rehabilitation options, but also give implications for the recommendations of exercise as a tool to prevent cardiovascular diseases in general.

5.1 The Exercise Intervention

As presented and described in the background section and in Table 3, there are still a limited number of RCTs that have investigated the effect of exercise in HTx recipients. Furthermore, most of them have compared some form of rehabilitation/exercise program with a control group not receiving any specific type of exercise strategy, and most of the exercise performed in the intervention groups have been performed in-hospital, at a moderate intensity. It is a big challenge running large-scale, high quality, in-hospital exercise studies, because the HTx recipients often live very far away from the transplantation centers, and it is difficult and expensive to recruit enough patients to participate in a long-term exercise program very far from their home. Our study is the largest published RCT in this field so far, and even though

Norway is a small country with a numerically, very small HTx population, this was manageable because we designed the intervention to be carried out individually, in each of the patients' home communities. Every participant was assigned to a local physical therapist, which was in close cooperation with our hospital and the PhD student in charge of the trial. As previously described, the exercise intervention, which lasted for one year, was divided into three main, intensive exercise periods with duration of 8 weeks each. After each 8-week period, the PhD student and the local physical therapist discussed the results and improvement so far, and made plans for the next intensive exercise period. This included HR analyses from the HR monitors and exercise logs, re-testing of the patient's maximum HR and adjustment of the desired training zones if necessary.

When the study first started, we were anxious to see whether this ambitious exercise intervention would and could be sustained by the participants for a full year. The results exceeded our expectations, showing that a mean of 96% of the planned exercise sessions were completed at target intensity throughout the year, without any adverse events. Thus, we feel it is safe to conclude that this form of exercise both is highly applicable and safe in stable, long-term HTx recipients.

Future large-scale studies are needed to confirm this, and HIIT also needs to be compared to other exercise strategies, not only a control groups receiving no particular training regimen. In our study, the control group was advised to continue with their usual weekly activities, but they did not undergo a specific exercise strategy designed by us, and the amount and type of exercise varied considerably. For our records, they reported their level of activity both at baseline and at follow-up.

5.2 Effect of high intensity interval training in HTx recipients

5.2.1 Peak oxygen uptake

The exercise group in our study improved their $\text{VO}_{2\text{peak}}$ level from 27.7 to 30.9 mL/kg/min, corresponding to 80% to 89% of predicted values in healthy subjects. These levels are high compared to most other studies describing $\text{VO}_{2\text{peak}}$ levels in HTx recipients to be between 50% and 70% of predicted (2;7;21;28) (Table 1). Our high baseline $\text{VO}_{2\text{peak}}$ values might be a result of selection bias, based on the design of the study, the exercise intervention and the inclusion criteria. This was also commented on by the reviewers of Paper III, but considering the wide range of $\text{VO}_{2\text{peak}}$ values (from 13.9 to 44.0 mL/kg/min, corresponding to 46 to 130% of predicted) and the normally distributed data, this rather suggests a heterogeneous group than a selected group of well fit HTx recipients, and the data might mirror the stable and healthy Norwegian HTx population quite well. Our high levels are supported by another recent Nordic RCT investigating the effect of high intensity exercise (16), which also demonstrates higher than average $\text{VO}_{2\text{peak}}$ values, with a baseline value of 23.9 improving to 28.3 mL/kg/min at follow-up, even with a considerably higher mean time after HTx of seven years versus four years in our study. Whether this could be an expression of Scandinavian HTx recipients having levels above average, or if it is due to type of test protocol and sub-maximal or maximal intensity reached during the exercise test protocol is uncertain.

The greatest limitation of our study, and other RCTs (Table 3), is that the control group did not undergo a specific exercise intervention, and therefore we cannot conclude that the HIIT program is superior to moderate intensity with respect to $\text{VO}_{2\text{peak}}$ increase. However, since the control group also performed a certain amount of exercise during the study period, according to general recommendations (67% exercised more than two times per week, and only 33% little or nothing); we believe that this HIIT program is likely to have induced a

greater effect than that of moderate training, which is in accordance with previous studies among patients with coronary artery disease (13) and left ventricular dysfunction (14), which have used a similar HIIT protocol.

At follow-up, the mean change in $\text{VO}_{2\text{peak}}$ between the groups in our study was 3.6 mL/kg/min. This is about the same as in three of the other RCTs presented in table 3 (6;31;34), but it is important to underscore that two of these (6;34) had considerably lower baseline $\text{VO}_{2\text{peak}}$ values, and it is well known that subjects with low, initial $\text{VO}_{2\text{peak}}$ levels easily gain greater improvements than those with fairly high baseline values (107).

Haykowsky et al. (31) demonstrated an improved mean $\text{VO}_{2\text{peak}}$ follow-up value in the exercise group close to ours (24.7 versus 30.9 mL/kg/min), and had a similar mean change between the groups of 3.5 mL/kg/min. This exercise intervention (31) also included elements of HIIT which makes a more justified comparison with our study. Haykowsky's study (31) was published in April 2009, and was, by the time we started including patients in our RCT in October the same year, the RCT with the highest demonstrated $\text{VO}_{2\text{peak}}$ improvement among HTx recipients. In 2011, during the course of our study, Hermann et al. (16) published the results of their study investigating effect of high intensity exercise in HTx recipients. They demonstrated an overwhelming difference of 5.6 mL/kg/min between the exercise group and the control group, after 8 weeks of exercising 3 times per week. Although it is questionable why and how the control group reduced their $\text{VO}_{2\text{peak}}$ level from 24.6 to 23.4 mL/kg/min in only 8 weeks, contributing to the large mean difference between the groups, the exercise group still had a remarkable mean improvement of 4.4 mL/kg/min, substantially supporting HIIT as a highly effective form of exercise in long-term HTx recipients. With our study also supporting HIIT as a safe, applicable and effective form of exercise, the field is now ready and in need of future studies investigating the effects of HIIT compared to other exercise interventions. Our study was unfortunately published too late to be included in the recent

systematic review and meta-analysis of exercise training in solid organ transplant recipients (108) which concludes that “exercise training is a promising but unproven intervention for improving the cardiovascular outcomes of solid organ transplant recipients”. This conclusion only underscores the great need for more research and larger RCTs in this field. We need to rethink our exercise strategies. The timing is also important, perhaps are the health benefits even greater if the intervention is started earlier; that is, shortly after HTx.

5.2.2 Chronotropic response

Chronotropic response is regarded an important factor influencing exercise capacity (6;23;40-42;46;47) and the reduced exercise capacity in HTx recipients is likewise generally associated with chronotropic incompetence due to denervation. Multiple studies showing partial normalization of the HR response have discrepant results regarding degree of normalization and percent of subjects developing normalization, in addition to great differences according the time after HTx when improved chronotropic response is confirmed. Bernardi et al. (6) showed that autonomic nervous control can be improved by physical training, while others have proposed that reinnervation may occur independently over time (4;109;110). In Paper I, we demonstrated a high degree of normalization of chronotropic responses documented as early as six months after HTx. This support the findings in one other study (10) but is both earlier discovered and with a higher degree of normalization than demonstrated by others (2;22;110-113). Our finding of a high percentage of normalized HR response in the intervention study (Paper III) is also in agreement with the high degree of normalization described in Paper I, during the first year after transplantation. The exercise group in the main study (Paper III) significantly improved their peak HR from 154 to 163 bpm, compared to the control group who remained unchanged (154 versus 153 bpm). This finding support Bernardi

et al. (6), but it is still unclear whether time alone may result in normalization of chronotropic responses or whether it is in combination with exercise or other factors.

It is assumed that chronotropic incompetence in HTx recipients is a limitation in order to adapt to interval training, and because of their atypical central and peripheral responses to exercise, the training regimens described have consisted mostly of steady state exercise with moderate intensity (4;38) (Table 3). Previously, only a couple of studies have described close to normal HR responses in HTx recipients (10;11). Adding our recent studies, increased evidence is now present suggesting HR response is not a limiting factor for exercise capacity in the majority of HTx patients. This finding will hopefully contribute to minimize the persistent exercise restrictions that apply to the denervated hearts.

A future challenge is finding answers to which factors influence the reinnervation process and why it is inconsistent and does not occur in all HTx subjects. In the 1990's statements like these were still published: "total denervation persists in the human heart following cardiac transplantation" (39) and "the lack of alteration in the heart rate response over time suggests that no significant functional reinnervation occurs" (25). Later, studies evaluating sympathetic and parasympathetic reinnervation still give somewhat contradicting answers, especially with respect to possible parasympathetic reinnervation (43;114-116). Evidence of sympathetic reinnervation seems to be more frequent and certain, but is inconsistent in nature (41;42;46;47;112;117). Different direct and indirect methods of evaluating reinnervation, such as heart rate variability analysis (118); cardiac release of noradrenalin (29); positron-emission tomography (PET) (47); and evaluation of chronotropic response as a sign of functional reinnervation, also show different results, although some of the methods tend to correlate (44).

Absence of parasympathetic activity is evident in the denervated heart with an elevated resting HR, often > 100 bpm (89). In addition to resting HR reflecting vagal tone, HR

recovery is also known as a marker of parasympathetic activity (119-122), whereas HR increase at onset of exercise and peak HR rather reflects sympathetic activity (27;89;123). The improved HR increase, and close to normal peak HR and HR reserve in our studies, support the notion of functional, sympathetic reinnervation. The improved HR recovery, as a marker of parasympathetic activity, support parasympathetic reinnervation, whereas the persistent elevated resting HR described in Paper I is *not* consistent with vagal reinnervation. Ergo, our results only confirm the inconsistency in the literature on reinnervation in general.

5.2.3 Central versus peripheral effects of exercise

Pulmonary diffusion, cardiac output and blood volume are regarded as the main central limitations to oxygen delivery, while the role of peripheral factors limiting $\text{VO}_{2\text{peak}}$ has been an object of greater discussion (124). It is agreed upon that $\text{VO}_{2\text{peak}}$ is dependent on the interaction of O_2 -transport and muscle (mitochondrial) consumption of O_2 . The dissension is rather about which of these is the main determinant (124). This, of course, may vary largely in trained versus sedentary subjects, or in different patient groups versus normal subjects. In athletes, as in patients with chronic lung disease, the pulmonary diffusion seems to be the greatest limitation. In healthy, untrained subjects and in patients with heart failure this is not the case; the principal limiting factor is cardiac output, often combined with skeletal muscle limitations (125). In HTx recipients, it is assumed that the reduced exercise capacity is due to a combination of central and peripheral physiological abnormalities (12;126;127), but the mechanisms behind the subnormal capacity is not completely understood. Thus, we initially hypothesized that a possible increase in $\text{VO}_{2\text{peak}}$ after the HIIT intervention would be subject to positive changes both centrally and peripherally. A collaborating PhD student, in charge of the echocardiographic measurements, performed thorough examinations of all the participants, using newer echocardiographic techniques, both at rest and during sub-maximal

exercise (bicycle ergometer). In contrast to documented improved cardiac function of HIIT, in patients with cardiovascular diseases in general (14;15;128), we, rather surprisingly, found no alterations of clinical importance, neither in cardiac systolic nor diastolic function as assessed by echocardiographic measurements (103). This suggests that HTx recipients respond differently to HIIT than other groups of patients.

Muscle diffusion capacity, mitochondrial enzyme levels and capillary density are other potential peripheral sites for $\text{VO}_{2\text{peak}}$ limitation (124). Although most research supports cardiovascular delivery to be the central component in $\text{VO}_{2\text{peak}}$, the importance of skeletal muscle function should not be under-estimated. As we found in Paper II, muscular exercise capacity and amount of body fat were the strongest factors predicting $\text{VO}_{2\text{peak}}$ in this group of HTx recipients. These findings are in accordance with Borrelli et al. (127) and were also confirmed in the main study, where the same peripheral factors made the most significant contributions to the improvement in $\text{VO}_{2\text{peak}}$. This suggests that peripheral muscular and metabolic alterations have a substantial impact on the aerobic exercise capacity in HTx recipients; maybe a greater impact than cardiac limitations.

However, despite the absence of detectable echocardiographic improvements in the current study, the HIIT group demonstrated a higher O_2 -pulse and lower HR at sub-maximal exercise levels, both indicating an increased stroke volume. In addition, the chronotropic response index (CRI), which reflects both the maximum HR and the resting HR, significantly increased from 0.89 to 0.95. The small number of observations, possibly causing a type 2 statistical error, may explain these somewhat contradicting findings regarding cardiac function. Echocardiographic measurements during peak exercise and a higher number of observations could perhaps reveal an undetected improvement in cardiac function.

Because of the initially high and close to normal CRI, and a mean time of 4 years after HTx, we did not expect any notable improvement in the chronotropic responses. Nevertheless,

at follow-up the HIIT group had significantly increased their CRI as a result of both a lower resting HR and a higher peak HR. It is still unclear whether improved autonomic nervous control is a result of exercise (6) or if it occurs independently, as a result of time (4;109). As previously mentioned, a large number of studies have documented partial sympathetic reinnervation, and it appears to be greatest the first few years after a HTx and then gradually decrease (4;42). The findings in the current study indicates that the peak HR, despite a close to normal level at baseline (four years post HTx), still can be influenced by intensive exercise and fully reach, or even exceed, the expected maximum HR. In the current study 30% of the patients had an expected maximum HR > 100 % (range 100-111%).

Vagal reinnervation is more disputed and only a few studies have documented signs of increased parasympathetic activity (43-45). However, HR recovery is well-known as a marker of parasympathetic influence (120;121), and values equal to or greater than 12 and 22 beats/min, after 1 and 2 min, respectively, is considered normal (89;90). In our study (Paper I), short term after HTx, there was a pronounced improvement in HR recovery during follow up, and in the intervention study, the HIIT group had a significant lower resting HR and a trend towards an improved HR recovery the first 30 sec of the recovery period, suggesting that exercise training may improve vagal reinnervation. This needs, however, to be confirmed in other intervention studies. To summarize, it seems quite clear that HTx recipients respond differently to exercise than other patient groups and that the beneficial training effects in our study predominantly rely on peripheral mechanisms and especially muscular exercise capacity. However, some of our findings also suggest some improvement in cardiac function, and the autonomic regulation is improved and close to normal. Further and more basal investigation is needed to establish why and how the transplanted hearts respond differently to high intensity exercise compared to healthy subjects or other patients groups.

5.2.4 Health related quality of life

In contrast to Sivertsen et al. (58) who found reduced HRQoL and higher frequency of anxiety and depression among HTx recipients from our center, compared to a reference population, both groups in our current study had high scores on HRQoL and no symptoms of anxiety or depression at baseline. This might be due to our inclusion criteria, allowing only stable and healthy HTx recipients to participate. The high baseline HRQoL scores in both groups limited the possibility of revealing an actual effect of exercise in this area. Despite the ceiling-effect, there was a clear trend towards a better overall HRQoL, in the HIIT group compared to the control group in all domains of the SF36 (Table 4). This was confirmed by the significantly higher rating on the VAS scale in the HIIT group, regarding their subjective opinion whether participation in this study generated positive influence on their own general health. This support previously documented evidence on the association between increased exercise capacity and better HRQoL (17;51;129).

5.2.5 Cardiac Allograft Vasculopathy

CAV continues to limit the long-term success of heart transplantation, and CAV in addition to malignancy are the most important causes of death in patients who survive the first year after HTx. The present study has to our knowledge, for the first time demonstrated that a one-year HIIT program decreases CAV progression in a group of stable HTx recipients, in addition to improved VO_{2peak} . A particular strength of the present study was the use of IVUS, which is considered the most sensitive tool for the diagnosis and progression of CAV (130). Serial IVUS measurements have considerable statistical power to detect small changes in the vessel wall. Although the clinical importance of the statistically significant, but numerically small difference may be questioned, the finding deserves attention given the widespread occurrence and therapeutic challenges in the treatment of established CAV.

Despite advances in CAV diagnosis, especially with IVUS, prevention and treatment of this disease is challenging, and current immunosuppressive protocols together with traditional cardio-protective drugs such as statins, ACE inhibitors and platelet inhibitors have shown little effect on disease progression. In the present study, CAV progression was reduced by more than 50% in the HIIT group compared to the control group. Although no previous reports on the effect of training on CAV progression in HTx patients exist, our finding is in accordance with effect of exercise on progression of coronary atherosclerosis among patients with CAD (131;132), and increased threshold for chest pain (133). The recent study by Yoshikawa et al. (131) showed that a high VO_{2peak} level was associated with healthier tissue composition and less coronary plaque in patients with CAD (131). Also, a recent review article summarizing the impact of exercise training on arterial wall thickness concludes that exercise can decrease arterial wall thickness in subjects with CAD or with cardiovascular risk factors, as well as in healthy subjects (132). However, what type of exercise, frequency, duration and intensity that give the best results remain to be determined.

In contrast to most studies investigating the effect of exercise on cardiovascular health, our study had a long-term, high intensity exercise intervention. If the effect on CAV is due to this mode of exercise is uncertain, but we believe a high intensity program is needed, given the fact that our control group must be considered a moderate training group as they performed a considerable amount of exercise during the study period (Only 33% exercised little or nothing and 67% 2 times or more per week). However, this needs to be confirmed in forthcoming studies.

Several mechanisms are involved in the initiation and progression of CAV including innate and adaptive immune responses as well as risk factors such as smoking, hypertension, hyperglycemia, hypercholesterolemia, BMI and metabolic disturbances (130). In our study (Paper IV), we found that the progression of CAV, as assessed by an increase in PAV > 1.5%

was associated with a significantly higher mean Δ weight, BMI and visceral fat (data not shown). Since a high BMI and visceral fat are associated with increased inflammation, which is a well known factor contributing to the development of endothelial dysfunction, atherosclerosis and CAV (134;135), a possible mechanism of HIIT on CAV progression could be mediated by reduction in the inflammatory burden. This would be consistent with studies among patients with CAD suggesting that the effect of exercise on atherosclerosis to some extent may be explained by its influence on metabolism and the anti-inflammatory effect of regular exercise (35;135;136). However, in the present study, except that the HIIT group had a significantly lower IL-8 level at follow-up (within group), a numerically lower level of CRP and a numerically higher level of IL-6, there was no clear effect of HIIT on the inflammatory mediators measured between the groups. This contrasts the findings of Hermann et al. (16), who carried out a comparable HIIT intervention and found a significant reduction of CRP in the HTx exercise group. The reason for the discrepant finding is unclear but could be related to patient population, duration of exercise or timing of blood sampling. We cannot rule out that exercise could have a beneficial effect on vascular inflammation not associated with a systemic inflammatory response. Less PAV increase was associated with a reduction in visceral fat as well as BMI and weight, and this could be due to an effect of HIIT on adipocyte-derived mediators, but this has to be clarified in forthcoming studies.

5.3 Limitations

Based on Paper III, the methodological quality of our study was recently rated according to the Jadad score, by the Centre for Evidence in Transplantation. The score was three out of a maximum score of five. The reason for the deducted score was that the study was not blinded. Studies with exercise interventions are of course more or less impossible to carry out blinded, but besides that, the greatest limitation of our study was that the control group did not

undergo a specific exercise strategy. The main reason for this was lack of resources, with the consequence that we can only state that HIIT is an effective and safe form of exercise, but not conclude that it is better than other types of training.

The inclusion criteria may also have led to a selection bias as the participants were all defined as healthy and stable and possibly had a higher motivation for exercise than those who refused to participate in the study. However, the baseline $\text{VO}_{2\text{peak}}$ values were normally distributed, ranging from 13.9 to 44.0 mL/kg/min, which indicate a heterogeneous group.

A major limitation in Paper IV is that this was designed as a sub-study and that the power calculations were performed based on a change in $\text{VO}_{2\text{peak}}$, rather than change in IVUS measurements. Furthermore, data were only present in 43 out of 52 HTx patients. The major reason for this was reduction in matched segments to analyze due to missing baseline or follow-up test. However, IVUS assessment was a pre-specified parameter, the effect was highly statistically significant and similar effects were seen on total or percent atherosclerotic burden, maximal intimal thickness and total plaque volume. We therefore believe that the effect is true, but the finding needs to be confirmed in other studies. Another factor that could be a confounding factor affecting the results, is that most baseline IVUS parameters were numerically, but not statistically, lower in the HIIT group compared to the control group, although progression of CAV (as measured by increased PAV and MIT) did not correlate with the baseline values (data not shown). We also divided the study population into baseline CAV category groups (Table 1, Paper IV) based on the angiography results (no stenosis / stenosis), and there were not any significant differences in the CAV progression between these two groups at follow-up (data not shown).

Furthermore, the small sample size may have influenced the ability to investigate the mechanisms behind the reduced CAV progression.

The greatest limitation in the study described in paper I, is the unconventional test method that was used; with the lack of an objective parameter of maximal effort possibly causing random differences in improved peak HR.

6. Conclusions

This thesis has investigated alterations in chronotropic responses during the first year after a heart transplant, and exercise capacity and the effect of high intensity interval based aerobic exercise training in long-term heart transplant recipients. The main conclusions are as follows:

1. The chronotropic responses to exercise improved substantially the first year after heart transplantation. Seventy-one percent of the study population developed a normalized heart rate response based on a maximum heart rate $> 85\%$ of age-predicted values. Based on these results the odds for normalization are 2.5 within the first year after heart transplantation.
2. Chronotropic incompetence was not a limiting factor for exercise capacity in a population of relatively fit heart transplant recipients. The most important factors determining VO_{2peak} were peripheral factors rather than cardiac function; with body fat and muscular exercise capacity as the most significant predictors.
3. High intensity interval based aerobic exercise training is an applicable, effective and safe way to improve VO_{2peak} , muscular exercise capacity and general health in stable, long-term heart transplant recipients.
4. A long-term high intensity interval training intervention strategy significantly reduced the progression of cardiac allograft vasculopathy among maintenance heart transplant recipients.

6.1 Implications for follow-up and future research

The high degree of normalization of the chronotropic responses taking place the first year after HTx, with the most significant changes developing within the first six months, should largely contribute to reduce the exercise restrictions that have applied to the denervated heart. Our findings suggest that chronotropic incompetence is *not* a factor limiting exercise capacity in the majority of HTx recipients. Furthermore, we have shown that a long-term HIIT intervention is a feasible, safe and effective way to improve exercise capacity and general health in stable, long-term HTx recipients. This form of exercise should be introduced and more frequently used among a broader audience. However, the transplanted heart seems to respond differently to this type of exercise, resulting mainly in peripheral improvements rather than improved cardiac function. Larger studies and more basal research are needed to investigate these mechanisms. Future research is also needed to see if the positive effects on CAV are reproducible, examine which mechanisms cause the effect, and whether such an intervention has an effect on long-term survival. At last, the important question regarding optimal timing for introducing HIIT after HTx should be assessed.

Figure 7
HIIT makes it possible to reach the peak!
One of the study participants at the top of Kattanakken, Norway, October 2010.
(The image is reproduced with permission from the person in the picture).

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