REVIEW

Exercise after heart transplantation: An overview

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Abstract

While life expectancy is greatly improved after a heart transplant, survival is still limited, and compared to the general population, the exercise capacity and health-related quality of life of heart transplant recipients are reduced. Increased exercise capacity is associated with a better prognosis. However, although several studies have documented positive effects of exercise after heart transplantation (HTx), little is known about the type, frequency and intensity of exercise that provides the greatest health benefits. Moreover, the long-term effects of exercise on co-morbidities and survival are also unclear. Exercise restrictions apply to patients with a denervated heart, and for decades, it was believed that the transplanted heart remained denervated. This has since been largely disproved, but despite the new knowledge, the exercise restrictions have largely remained, and up-to-date guidelines on exercise prescription after HTx do not exist. High-intensity, interval based aerobic exercise has repeatedly been documented to have superior positive effects and health benefits compared to moderate exercise. This applies to both healthy subjects as well as in several patient groups, such as patients with metabolic syndrome, coronary artery disease or heart failure. However, whether the effects of this type of exercise are also applicable to heart transplant populations has not yet been fully established. The purpose of this article is to give an overview of the current knowledge about the exercise capacity and effect of exercise among heart transplant recipients and to discuss future exercise strategies.

Core tip: It is time to rethink exercise strategies among heart transplant populations. Chronotropic incompetence is not necessarily a factor that limits exercise capacity in heart transplant recipients, and the exercise restrictions that have traditionally been applied to patients with a denervated heart can be disregarded. High-intensity, interval-based aerobic exercise is superior to moderate exercise in patients with coronary artery disease and heart failure, and the positive effects of this type of exercise seem to also be largely reproducible among heart transplant recipients.

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INTRODUCTION

Heart transplantation (HTx) gives numerous patients with end-stage heart disease a second chance at life. However, although life expectancy is greatly improved, survival is reduced, mainly due to the increased frequency of late complications. Additionally, the patient's exercise capacity and health-related quality of life (HRQoL) are reduced compared with the general population[1]. Exercise capacity improves after a HTx when compared with end-stage heart failure[2-8], but continues to be subnormal when

compared with age-matched values in healthy individuals. In most studies, the peak oxygen uptake (VO_{2peak}) levels range from 50% to 70% of the general population (Table 1), and a reduced VO_{2peak} level is generally associated with a poorer prognosis[9]. Only a few studies have reported individuals reaching close to normal VO_{2peak} levels[10,11]. Both central hemodynamics and peripheral physiological abnormalities may explain the reduced exercise capacity of these patients (Table 2). These factors include reduced cardiac output due to chronotropic incompetence or reduced stroke volume, peripheral abnormalities, including reduced muscle strength and oxidative capacity, and abnormal blood supply due to impaired vasodilatory capacity or capillary density[12].

While several studies have demonstrated an effect of aerobic exercise after HTx, the majority of studies 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". High-intensity interval training (HIT) has repeatedly proven to be a highly efficient form of exercise for improving the physical capacity of both normal subjects and patients with coronary artery disease (CAD) and heart failure[13-15]. While the exact results in various patient groups are varied, HIT has demonstrated improvements 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 two small studies published in 2004 and 2011[11,16], HIT has not been used as an intervention among HTx recipients. A systematic review and meta-analysis regarding the effects of exercise in solid organ transplant recipients were recently published[17], concluding that "exercise training is a promising but unproven intervention for improving cardiovascular outcomes of solid organ transplant recipients". Because the existing randomized controlled trials (RCTs) are small and of relatively short duration, more large-scale RCTs are urgently needed to develop clear and evidence-based guidelines regarding exercise prescriptions after HTx.

The most recent RCT assessing effect of exercise after HTx[18], which was also the largest to date, was published too late to be included in that systematic review regarding the effects of exercise in solid organ transplant recipients[17], but the study is presented in Table 3 and will be referred to throughout this article.

TRANSPLANTED, DENERVATED HEART

In contrast to the chronotropic response of a normal heart to exercise, a newly transplanted heart is denervated, which causes higher resting heart rate (HR) and reduced HR response (chronotropic incompetence)[8]. The HR response during exercise is mainly controlled by catecholamines from the adrenal glands, resulting in a sig-

nificantly slower increase of the HR at onset of exercise, a reduced peak HR, and a delayed return towards resting values after cessation of exercise[4,8,19-21]. It is a common belief that this slow HR is of great importance when designing rehabilitation programs early after HTx, especially during the very first year. An improved HR response to exercise has been demonstrated during the first year after surgery[21], but it is unclear if this is due to reinnervation, and if so, what the functional importance of possible reinnervation is[22-24].

EXERCISING WITH A TRANSPLANTED HEART

Knowledge about the denervated heart is important in order to adjust the exercise protocol to achieve the optimal effect of physical exercise. There are several small studies which have shown that aerobic exercise gives a higher exercise capacity in HTx recipients[3,5,6,25-28]. The exercise protocols used, which have mainly consisted of steady-state training with moderate intensity, have shown positive effects[3,5,6,26-28]. However, the increase in exercise capacity and the VO_{2peak} levels reached are moderate[3,5,6,26-28].

Several reports have been published on the effects of rehabilitation and exercise in non-transplant patients. The main conclusion is that high-intensity, aerobic training, especially interval-based training, is a favorable type of exercise that yields improvements in both peripheral and central factors[13,14,29]. Wisløff *et al*[14] showed that interval training improved VO_{2peak} with 46% in patients with heart failure, but it has been unclear whether this type of exercise is suitable for HTx patients.

It is assumed that the delayed HR response after HTx is a limitation in regard to adapting to interval training. Presently, it is commonly believed that because of the slow HR of these patients, the session should begin with a thorough warm-up period, which should be followed by steady-state (Steady-state training refers to no rapid changes in intensity or exercising with an even HR) 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 in joining existing rehabilitation programs in their home environment. Additionally, it has not yet been thoroughly investigated if this form of exercise is really unsuitable for this group of patients.

MECHANISMS OF REDUCED EXERCISE CAPACITY AMONG HEART TRANSPLANT RECIPIENTS

Both central hemodynamic and peripheral physiological factors most likely contribute to the reduced exercise capacity in HTx recipients (Table 2). The central factors

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

Study	n	Mean age (yr)	Mean time after HTx	VO$_{2peak}$: mL/kg per minute or L/min	VO$_{2peak}$ (% of age-predicted value)	Percent of age-predicted HR$_{max}$ or actual HR$_{max}$ (bpm)
Renlund *et al*[123]	110	51 ± 10	26 mo	17.7 ± 0.3 mL	64% ± 1%	85%
Mandak *et al*[51]	60	52 ± 10	1 yr	16.2 ± 3.8 mL	NA	137 ± 24
Osada *et al*[124]	56	50 ± 12	3 yr	20.0 ± 5.0 mL	70% ± 17%	88% ± 11%
Notarius *et al*[12]	12	51 ± 4	8 mo	17.3 ± 1.7 mL	57%	147 ± 7
Douard *et al*[30]	85	52 ± 12	0-100 mo	21.1 ± 6 mL	NA	85% ± 13%
Squires *et al*[24]	95	48 ± 14	1 yr	19.9 ± 4.8 mL	61% ± 15%	138 ± 22
Gullestad *et al*[48]	174	51 ± 1	3.5 yr	19.4 ± 0.4 mL	70% ± 1%	146 ± 2
Myers *et al*[125]	47	47 ± 12	4.8 yr	9.4 ± 2.6 mL	59% ± 14%	129 ± 18
Schmid *et al*[126]	17	58 ± 13	65 ± 27	20.9 ± 5.2 mL	NA	136 ± 12
Richard *et al*[127]	7	40 ± 13	2 yr	NA	101% ± 12%	93% ± 9%
Carter *et al*[2]	47	48	5 yr	16.1 ± 0.5 mL	51% ± 1.5%	74% ± 1%
Ulubay *et al*[118]	7	43 ± 14	19 mo	1.45 ± 0.33 L	NA	114 ± 41

HTx: Heart transplant; HR$_{max}$: Maximum achieved heart rate; bpm: Beats per minute; NA: Not available.

Table 2 Possible mechanisms associated with reduced exercise capacity in heart transplant recipients

Central factors
  Reduced cardiac output
    Chronotropic incompetence
    Reduced stroke volume
    Systolic dysfunction
    Diastolic dysfunction
  Pulmonary dysfunction
    Pulmonary hypertension
    Lung disease
    Pulmonary congestion
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
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 health-related quality of life

include chronotropic incompetence, impaired LV function or greater arteriovenous oxygen difference, while peripheral limitations 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 immunosup-pressive regimens, 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 their reduced performance[7,12,20,30-33] (Table 2).

HIT

The American College of Sports Medicine[34] and American Heart Association[35] recommend exercising with an intensity between 50% and 90% of maximum VO$_2$, which refers to approximately 60%-95% of the maximum HR. In comparison to the detailed prescription of different medications, this is a very imprecise recommendation. As such, it causes difficulties for both the health personnel who are obligated to give advice based on these recommendations, and the patients who are trying to carry out these vague exercise prescriptions. One of the reasons for the imprecise recommendations is that there has been uncertainty and disagreement regarding how VO$_{2peak}$ improves most efficiently. The majority of researchers in the field now agree that the major factor limiting an individual's VO$_{2peak}$ is the stroke volume. Given that maximum HR cannot be increased, the stroke volume is the limiting (and only) factor that, through exercise, may improve cardiac output[36]. It is reasonable to think that exercising at a near to maximum stroke volume would give the best results. The previous belief was that maximum stroke volume was reached at approximately 50%-70% of maximum HR[37,38], and this is still stated in most textbooks[36], even though it was shown as early as in the 1960s that stroke volume does not necessarily plateau in this range[39]. Additional and more recent research has documented, both in untrained, moderate and well trained subjects, that the stroke volume often does not reach a plateau until the HR is close to its maximum[40-44]. This has not been documented in patients with CAD, but several studies of high-intensity exercise interventions have documented a superior effect of such exercise compared to exercise at a moderate intensity, both in patients with heart failure and CAD[13,14,45-47].

Table 3 Summary of randomized controlled trials investigating the effect of exercise in heart transplant recipients

Study	*n*, mean age (yr)	Mean time after HTx	Intervention	Mean change in VO$_{2peak}$ (mL/kg per minute) within groups	Mean change in VO$_{2peak}$ (mL/kg per minute) between groups
Kobashigawa *et al*[3]	27, 52	1 mo	6 mo partly supervised rehabilitation program *vs* controls CG	Ex: 9.2 → 13.6	2.5
			Walking: cycling and upper and lower limb exercises for 30 min × 1-3/wk	Con: 10.4 → 12.3	
Tegtbur *et al*[26]	32, 55	5 yr	1 yr home-based exercise program *vs* controls	Ex: 18.6 → 20.0	1.3
			Cycling every other day for 1 yr at 80%-90% of maximum HR	Con: 18.9 → 19.0	
Bernardi *et al*[6]	24, 52	6 mo	6 mo home training *vs* controls	Ex: 14.9 → 19.6	3.4
			Cycling at 60%-70% of VO$_{2peak}$ 30 min × 5/wk × 6 mo	Con: 14.3 → 15.6	
Karapolat *et al*[5]	28, 42	1.5 yr	8 wk supervised hospital training *vs* home-based training		3.4
			1.5 h of multiple exercises: including aerobic exercise for 30 min at 60%-70% of VO$_{2peak}$ × 3/wk	Ex: 16.7 → 19.5	
			The controls received written guidelines on exercises and a walking program	Con: 20.1 → 19.5	
Wu *et al*[27]	37, 56	2 yr	8 wk home training *vs* controls	Ex: 12.1 → 13.2	1.6
			Strength training and aerobic exercise at 60%-70% of VO$_{2peak}$: 35-40 min × 3/wk	Con: 13.7 → 13.2	
Haykowsky *et al*[25]	43, 59	5 yr	12 wk aerobic/strength training *vs* controls		
			First 8 wk: continuous aerobic exercise at 60%-80% of VO$_{2peak}$: 30-45 min × 2/wk		
			Continuous aerobic training at 80% of VO$_{2peak}$, 45 min × 2/wk and bicycle interval training for 30 s at 90%-100% of VO$_{2peak}$: followed by 60 s rest for 10-25 reps × 2/wk in the final 4 wk	Ex: 21.2 → 24.7	3.5
			Resistance training at 50% of 1RM: 10-15 reps × 1-2 sets × 4 exercises × 2/wk for 12 wk	Con: 18.2 → 18.2	
Hermann *et al*[16]	27, 50	7 yr	8 wk high-intensity interval training *vs* controls		5.6
			Interval blocks of 4 min/2 min/30 s: corresponding to 80%: 85% and 90% of VO$_{2peak}$: respectively: and recovery periods of ½ min: and finally staircase running at 80% of VO$_{2peak}$: followed by recovery walking 60 min × 3/wk	Ex: 23.9 → 28.3 Con: 24.6 → 23.4	
Nytrøen *et al*[18]	48, 51	4 yr	1 yr high-intensity interval training *vs* controls		3.6
			4 interval blocks of 4 min each performed at 91% of peak HR: with 3 min active recovery periods between each block	Ex: 27.7 → 30.9	
			3 periods of 8 wk distributed throughout 1 yr with exercise 3/wk for a total of 72 exercise sessions	Con: 28.5 → 28.0	

HTx: Heart transplant; NT: No training; Ex: Exercise group; Con: Control group; 1RM: 1 repetition maximum; HR: Heart rate.
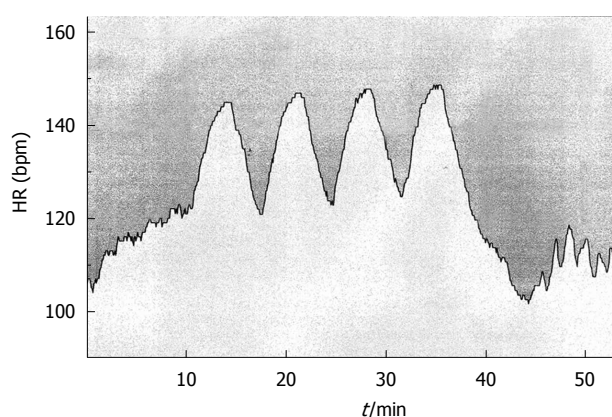
Figure 1 Example of a 4 x 4 high-intensity interval training session performed by a heart transplant recipient.

Most individuals should be able to reach an intensity of approximately 90%-95% of their maximum HR within 1-2 min. Based on this, the leading research community of this field in Norway (Norwegian University of Science and Technology, Trondheim) have proposed and documented that 4 exercise bouts of 4 min each (4 × 4) (Figure 1), with an active break in between, is an exercise prescription that is highly effective and works very well[38].

HIT IN HEART TRANSPLANT RECIPIENTS

As shown in Table 3, only a limited number of RCTs have investigated the effect of exercise in HTx recipients. Furthermore, most of these studies compared some form of rehabilitation/exercise program with a control group that was not receiving any specific type of exercise strategy, and most of the exercises performed in the intervention groups were performed in-hospital and at a moderate intensity. It is challenging to conduct 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 away from their home. Thus, a training program that is close to the patients' home might be more desirable. We tested such an approach in a study investigating the effect of HIT in HTx recipients[18], and even though Norway is a small country with a very small

HTx population, this was manageable because we designed the intervention to be carried out individually, in each of the patients' home communities.

Each participant was assigned to a local physical therapist who cooperated closely with our hospital and the people in charge of the trial. The exercise intervention, which lasted for 1 year, was divided into three main, intensive exercise periods lasting 8 wk each. After each 8-wk period, the project group and the local physical therapist discussed the results and the improvements in each individual patient thus far and made plans for the next intensive exercise period. The evaluation of the training period 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 fairly ambitious exercise intervention would and could be sustained by the participants for a full year. Of the 52 patients who were initially recruited, 48 completed the follow-up, and the results exceeded our expectations, showing that a mean of 96% of the planned exercise sessions were completed at the target intensity throughout the year, without any adverse events. Four patients did not complete the study due to other reasons. Thus, we feel that it is safe to conclude that this form of exercise is both highly applicable and safe in stable, long-term HTx recipients[18]. Our results are in accordance with the only other two existing studies that introduced HIT to HTx recipients[11,16], but future large-scale studies are needed to confirm the observed effects on peak exercise capacity and determine the mechanisms by which this occurs. Additionally, the studies should examine whether HIT has beneficial effects besides improving exercise capacity, such as in reducing transplant related complications. Furthermore, HIT also needs to be compared to other exercise strategies and not only control groups receiving no particular training regimen.

EFFECT OF EXERCISE IN HEART TRANSPLANT RECIPIENTS

The first RCT investigating the effect of exercise in HTx recipients was published by Kobashigawa *et al*[3]. The trial included patients who were 1 mo post HTx and compared a 6-mo 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 per minute ($P < 0.001$), but the VO_{2peak} level reached at the end of the intervention was low compared to the values predicted for healthy subjects of similar age and sex. This was also reflected in most of the subsequent trials. Table 3 describes the details of the published RCTs during the period from 1999 to 2012. The mean VO_{2peak} values reached after the exercise interventions ranged from 13.2 to 28.3 mL/kg per minute in the various studies, and the mean change between the control and exercise groups ranges from 1.3 to 5.6 mL/kg per minute. Except from the two previously mentioned randomized HIT-stud-

ies[16,18], the mean intensity of the aerobic training was reported to be 60%-80% of VO_{2peak} in the majority of the studies, the exercise duration ranged from 30 min to 1.5 h, 2-5 times per week for 8 wk up to 1 year, the mean time after HTx ranged from 1 mo up to 7 years, and the number of participants ranged from 24 to 43 (Table 3).

Based on the great differences between these trials, the somewhat inconsistent results and the lack of a control group undergoing a different exercise strategy in most of the RCTs, it can only be concluded that exercise improves VO_{2peak}; it is not yet possible to state which type of exercise, intensity and duration gives optimal results, although a HIT-intervention seems to be favorable.

Most of the studies describing VO_{2peak} levels in HTx recipients reported that the levels to be between 50% and 70% of predicted values[2,7,20,48]. The highest level reported was from a study carried out at our center[18]. The exercise group improved their VO_{2peak} level from 27.7 to 30.9 mL/kg per minute, corresponding to 80% to 89% of predicted values in healthy subjects (Table 1). The high baseline VO_{2peak} values may have been a result of selection bias, based on the design of the study, the exercise intervention and the inclusion criteria. However, considering the wide range of VO_{2peak} values (from 13.9 to 44.0 mL/kg per minute, corresponding to 46% to 130% of predicted) and the normally distributed data, this suggests a heterogeneous group rather 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 in HTx recipients[16]. In that study, the authors demonstrated higher than average VO_{2peak} values, with a baseline value of 23.9 improving to 28.3 mL/kg per minute at follow-up, even with a considerably higher mean time after HTx of 7 years *vs* 4 years in our study. It is unclear whether this could be a reflection that Scandinavian HTx recipients have levels above average, or if it is due to type of test protocol used in other studies and/or uncertainty about whether maximal intensity really was reached during the exercise test. However, we believe that HIT interventions[16,18] likely induced a greater effect than moderate training. This is in accordance with previous studies among patients with CAD[13] and left ventricular dysfunction[14], which have used comparable HIT protocols.

At follow-up, the mean change in VO_{2peak} between the groups in our study[18] was 3.6 mL/kg per minute. This is similar to three of the other RCTs involving moderate training that are presented in Table 3[6,25,28]. However, it is important to note that two of these studies[6,28] had considerably lower baseline VO_{2peak} values and that it is well known that subjects with low initial VO_{2peak} levels easily gain greater improvements than those with fairly high baseline values[49]. Haykowsky *et al*[25] demonstrated a similar improved mean VO_{2peak} follow-up value in the exercise group (24.7 mL/kg per minute *vs* 30.9 mL/kg per minute) and reported a similar mean change between the groups of 3.5 mL/kg per minute. This exercise inter-

vention[25] also included elements of HIT, which makes a more suitable comparison for our study. Haykowsky's study[25], which was published in April 2009, the same year we started including patients in our RCT, was then the RCT with the highest demonstrated VO$_{2peak}$ improvement among HTx recipients. In 2011, during the course of our study, Hermann et al[16] published the results from their study, demonstrating an overwhelming difference of 5.6 mL/kg per minute between the exercise group and the control group after 8 wk of exercising 3 times per week. Although it is questionable why and how the control group reduced their VO$_{2peak}$ level from 24.6 to 23.4 mL/kg per minute in only 8 wk, which contributed to the large mean difference between the groups, the exercise group still had a remarkable mean improvement of 4.4 mL/kg per minute, substantially supporting HIT as a highly effective form of exercise in long-term HTx recipients. Similarly, our study supports HIT as a safe, applicable and effective form of exercise, and the field is now ready and in need of future studies investigating the effects of HIT compared to other exercise interventions. The timing is also important, as the health benefits may be even greater if the intervention is started earlier, that is, shortly after HTx.

Chronotropic responses and reinnervation

In the 1990s, it was widely believed that "total denervation persists in the human heart following cardiac transplantation"[50] and "the lack of alteration in the HR response over time, suggests that no significant functional reinnervation occurs"[51]. This was the common belief in most research communities in early studies among HTx recipients. However, in last decade, a body of evidence has repudiated this statement. Nevertheless, several studies evaluating sympathetic and parasympathetic reinnervation have yielded somewhat contradicting results, especially with respect to possible parasympathetic reinnervation[52-56]. The evidence of sympathetic reinnervation seems to be more frequent and certain, but is inconsistent in nature[57-63]. Multiple different direct and indirect methods of evaluating reinnervation, such as HR variability analysis[64], cardial release of noradrenalin[22], positron-emission tomography[65] and the evaluation of the chronotropic response as a sign of functional reinnervation, have also yielded varying results[66].

The normalization of the chronotropic responses is associated with functional reinnervation and better exercise capacity[6,30,57-60,65]. Along the same lines, the reduced exercise capacity in HTx recipients is generally associated with chronotropic incompetence due to denervation. Multiple studies showing partial normalization of the HR response have reported discrepant results regarding the degree of normalization and percent of subjects developing normalization, in addition to great differences according the time after HTx when the 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 rein-nervation occurs independently over time[4,61,67]. Richard et al[10] and Pokan et al[11] have shown peak HR values close to or above age-predicted in HTx recipients. These findings are supported by a study from our center[21], in which we documented a high degree of normalization of chronotropic responses within 6 mo after HTx. This occurred earlier and with a higher degree of normalization than demonstrated by others[2,24,62,67-69]. The high degree of normalization during the first year after HTx[21] was confirmed in a different long-term HTx population in the previously discussed HIT-intervention study[18]. The exercise group in this study significantly improved their peak HR from 154 to 163 bpm, whereas the control group remained unchanged (154 bpm vs 153 bpm). This finding supports Bernardi et al[6], but it is still unclear whether time alone may result in the normalization of chronotropic responses or whether it occurs in combination with exercise or others factors.

Because it has been assumed that chronotropic incompetence in HTx recipients is a limitation towards adapting to interval training, and because the patients have atypical central and peripheral responses to exercise, previously described training regimens have mostly consisted of moderate, steady-state intensity exercise[4,17,32] (Table 3). Only a few previous studies have described close to normal HR responses in HTx recipients[10,11]. These, together with our recent studies[18,21], have provided increasing evidence suggesting that HR response is not a limiting factor for exercise capacity in the majority of HTx patients. Hopefully, this finding will contribute to minimizing the persistent exercise restrictions that apply to patients with denervated hearts. A future challenge is to identify which factors influence the reinnervation process and why it is inconsistent and does not occur in all HTx subjects.

The absence of parasympathetic activity is clearly evident in the denervated heart, which has an elevated resting HR, often more than 100 bpm[70]. Resting HR reflects vagal tone and HR recovery is known to be a marker of parasympathetic activity[71-74] while HR increase at onset of exercise and peak HR reflect sympathetic activity[19,70,75]. The improved HR increase and close to normal peak HR and HR reserve observed in several studies[10,11,18,21] support the notion of functional, sympathetic reinnervation. In one of our studies[21], we found improved HR recovery, a marker of parasympathetic activity[70,72,73,76], thus suggesting parasympathetic reinnervation. In contrast, persistent elevated resting HR[21] was not consistent with vagal reinnervation. Although we also found a significant lower resting HR in another study[18], suggesting improved vagal reinnervation, our results only confirm the inconsistencies in the literature regarding reinnervation in general.

Central vs 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 VO$_{2peak}$ has been an object of greater discussion[77]. While it is agreed upon that VO$_{2peak}$ is dependent on the interac-

tion between O_2-transport and muscle (mitochondrial) consumption of O_2, there is disagreement as to which of these is the main determinant[77]. The results vary largely in trained *vs* sedentary subjects or in different patient groups *vs* normal subjects. In athletes, as in patients with chronic lung disease, pulmonary diffusion seems to be the greatest limitation. In healthy, untrained subjects and in patients with heart failure, the principal limiting factor is cardiac output, often combined with skeletal muscle limitations[78]. In HTx recipients, it is assumed that reduced exercise capacity is due to a combination of central and peripheral physiological abnormalities[12,79], but the mechanisms behind this subnormal capacity is not completely understood. Thus, we initially hypothesized in our recent trial[18,80] that a possible increase in VO_{2peak} after a HIT intervention would be positively affected by both central and peripheral factors. To study myocardial performance, we performed thorough examinations of the systolic and diastolic function of all participants using newer echocardiographic techniques, both at rest and during sub-maximal exercise (bicycle ergometer). In contrast to the documented improved cardiac function of HIT in patients with cardiovascular diseases in general, we found, rather surprisingly, no alterations of clinical importance, either in cardiac systolic or diastolic function as assessed by echocardiographic measurements[80]. This suggests that HTx recipients respond differently to HIT than other groups of patients. Muscle diffusion capacity, mitochondrial enzyme levels and capillary density are other potential peripheral sites for VO_{2peak} limitation[33,77]. Although most research supports cardiovascular delivery as the central component in VO_{2peak}, the importance of skeletal muscle function should not be underestimated[33]. Borrelli *et al*[82] found that the main gain in VO_{2peak} was at the peripheral level. In accordance with this, we found that muscular exercise capacity and amount of body fat were strong factors predicting VO_{2peak} in a group of HTx recipients[83]. These findings were confirmed in a follow-up study[18], where the same peripheral factors made the most significant contributions to the improvement in VO_{2peak}. These findings suggests that peripheral muscular and metabolic alterations have a substantial impact on the aerobic exercise capacity in HTx recipients and that they may have a greater impact than cardiac limitations[33].

However, despite the absence of detectable echocardiographic improvements in the current study[80], the HIT group demonstrated a higher O_2-pulse and lower HR at sub-maximal exercise levels, which indicate 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. These somewhat contradictory findings regarding cardiac function may be explained by the small number of observations, possibly causing a type 2 statistical error. Echocardiographic measurements during peak exercise and a higher number of observations could reveal an undetected improvement in cardiac function in future studies.

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 HIT group showed a significant increase in their CRI as a result of both a lower resting HR and a higher peak HR[18]. However, 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[4,63]. As previously mentioned, a large number of studies have documented partial sympathetic reinnervation. This appears to be greatest during the first few years after a HTx and then gradually decreases[4,59]. The findings in our study[18] indicate that the peak HR, despite a close to normal level at baseline (4 years post HTx), can still be influenced by intensive exercise and fully reach, or even exceed, the expected maximum HR. A total of 30% of the patients in the current study had an expected maximum HR > 100% (range 100%-111%).

In summary, it seems quite clear that HTx recipients respond differently to exercise than other patient groups and that the beneficial training effects in a number of studies[18,25,82] predominantly rely on peripheral mechanisms, especially muscular exercise capacity. However, some of the findings in our study[18] also suggest some improvements in cardiac function and that autonomic regulation is improved and close to normal. Further investigation is needed to establish why and how the transplanted hearts respond differently to high-intensity exercise than normal subjects and other patients groups.

EFFECT OF EXERCISE ON TRANSPLANT RELATED COMPLICATIONS

It is well known that many HTx recipients develop a number of complications, such as cardiac allograft vasculopathy (CAV), graft failure, renal failure, cancer, gout, metabolic disturbances, including hyperlipidemia and diabetes mellitus, and reduced HRQoL. These may all contribute to increased morbidity and reduced survival. In general, exercise might have beneficial effects on several of these parameters in the general population and in different patients groups. However, little is known about the role of exercise on transplant related complications. The few RCTs that have been published[17,32] (Table 3) have mainly documented the effects of exercise on exercise capacity, muscle strength, body composition, endothelial function, some inflammatory biomarkers and HRQoL. However, detailed knowledge regarding other effects of exercise, such as on metabolic disturbances, renal function and co-morbidities, does not exist. Studies describing factors associated with exercise capacity also provide limited and uncertain information because the specific factors considered varies greatly[30,31,48,83].

We recently examined the effect of HIT on CAV[84]. CAV (Figure 2) is a rapidly progressive form of atherosclerosis that occurs in HTx recipients and involves diffuse thickening and occlusion of the coronary arteries[85]. The classic early sign of CAV, intimal thickening, is present in approximately 58% of the arteries during the first year
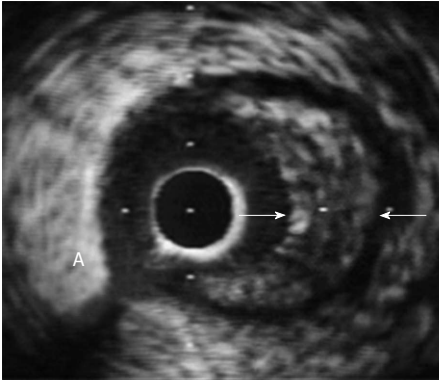
Figure 2 Intravascular ultra sound increases the sensitivity for early diagnosis of cardiac allograft vasculopathy compared to traditional angiography. Diffuse intimal thickening (area between the arrows) can be accurately identified by intra vascular ultra sound in contrast to angiography where only the lumen size is visible.

after HTx[86,87]. Later, luminal stenosis of the epicardial branches and occlusion of the smaller arteries develop, resulting secondarily in myocardial ischemia and infarction[88]. Treating 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[85,88]. Because of denervation, myocardial ischemia may be asymptomatic in many cases, and CAV can only be diagnosed by coronary angiography or intravascular ultra sound (IVUS). IVUS increases the sensitivity for early diagnosis compared to traditional angiography[85] (Figure 2).

Existing therapy options, both for the prevention and treatment of CAV, including immunosuppressive drugs and statin therapy early after HTx, have so far not given the desired results[88-90]. In clinical practice, prophylaxis of CAV involves modification of general risk factors, such as smoking, obesity, diabetes and hypertension, as well as the implementation of physical activity[91]. However, although the atheroprotective effect of exercise and the effect of physical activity on established CAD is well documented[92-94], with HIT being reported to have a more pronounced effect[14,38], knowledge about the specific effect of exercise on CAV is very limited.

CAV continues to limit the long term success of HTx; CAV is, in addition to malignancy, the most important causes of death in patients who survive the first year after HTx. In our recent study[84], we demonstrated, using serial IVUS measurements, that the progression of CAV was reduced by more than 50% in the HIT group compared to the control group[84]. Although no previous reports on the effect of exercise on CAV progression in HTx patients exist, our finding is in accordance with the effect of exercise on progression of coronary atherosclerosis among patients with CAD[95,96], specifically, an increased threshold for chest pain[97]. In a recent study by Yoshikawa *et al*[95], it was shown that a high VO_{2peak} level was associated with healthier tissue composition and less coronary plaque in patients with CAD. Additionally, a recent review article summarizing the impact of exercise training on arterial wall thickness concluded that exercise can decrease arterial wall thickness in subjects with CAD or with cardiovascular risk factors, as well as in healthy subjects[96]. However, what type of exercise, frequency, duration and intensity that gives the best results remain to be determined.

In contrast to most studies investigating the effect of exercise on cardiovascular health, our study[84] had a long-term, high-intensity exercise intervention. If the effect on CAV is due to this mode of exercise is uncertain and needs to be confirmed in future studies. However, we believe that a high-intensity program is needed, given that the control group in our study must be considered a moderate training group as they performed a considerable amount of exercise during the study period. Specifically, only 33% exercised little or not at all, and 67% exercised 2 times or more per week.

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, body mass index (BMI) and metabolic disturbances[98]. In our study, we found that the progression of CAV, as assessed by an increase in percent atheroma volume (PAV) > 1.5%, was associated with a significantly higher mean change in weight, BMI and visceral fat. Because 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[99], a possible mechanism by which HIT affects CAV progression could be mediated by a reduction in the inflammatory burden. This is consistent with studies among patients with CAD that have suggested that the effect of exercise on atherosclerosis may be explained, to some extent, by its influence on metabolism and its anti-inflammatory effects[100,101]. However, in the present study[84], other than significantly lower IL-8 level at follow-up (within-group), a numerically lower level of C-reactive protein (CRP) and a numerically higher level of IL-6 in the HIT group, there was no clear effect of HIT on the differential expression inflammatory mediators between the groups. This contrasts the findings of Hermann *et al*[16], who carried out a comparable HIT 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 that is not associated with a systemic inflammatory response. Lower increases in PAV were associated with a reduction in visceral fat, as well as BMI and weight[84], which could be due to an effect of HIT on adipocyte-derived mediators. This needs to be clarified in future studies.

Health related quality of life
Studies investigating HRQoL after HTx have clearly demonstrated that HTx recipients have significantly improved HRQoL compared to the pre transplant stage[102-107]. These studies have mainly used generic questionnaires or

a combination of generic and disease specific question-naires[102-107]. Several studies have reported that the improved HRQoL also remains high in the long-term after HTx[102,103,108-111]. In contrast, we previously found reduced HRQoL among HTx patients in the long term after surgery compared with newly transplanted patients[112]. Compared with HRQoL scores in general populations, HTx populations demonstrate varied results. Some studies report no HRQoL differences between HTx recipients and the general population[106,110,111], whereas others have reported that HTx populations have significantly lower HRQoL scores compared with a reference population[103,108,109,112-116]. Furthermore, reduced HRQoL is associated with anxiety and depression after HTx[105,107,114,117].

In contrast to the previous study from our center demonstrating a higher frequency of depression and anxiety[112], both groups in the most recent study from our center had high scores on HRQoL and no symptoms of anxiety or depression at baseline[18]. This might be due to our inclusion criteria, allowing only stable and healthy HTx recipients to participate. The high baseline HRQoL scores among both groups limited the possibility of revealing an actual effect of exercise in this area, but despite the ceiling-effect, there was a clear trend towards a better overall HRQoL in the HIT group compared to the control group in all domains of SF36[18]. This was also confirmed by a significantly higher rating in the HIT group on the VAS scale, which assessed their subjective opinion on whether participation in the HIT intervention generated positive influences on their general health[18]. This supports previously documented evidence on the association between increased exercise capacity and better HRQoL[105,118-122].

SUMMARY AND IMPLICATIONS FOR FOLLOW-UP AND FUTURE RESEARCH

In the past few years, there has been increasing focus on using physical exercise as a tool in both the 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 great benefits of regular exercise, it is still underutilized as a therapeutic intervention.

Traditionally, several exercise restrictions have applied to the transplanted, denervated heart, which seems to be based more on caution than scientific evidence. The time seems to be right for rethinking the use of exercise among HTx recipients and to offer an "up to date" physical training principle to this group of patients who are presently not recommended to participate in HIT programs.

The high degree of normalization of chronotropic responses among HTx recipients should be a major factor in support of reducing the exercise restrictions that have applied to the denervated heart. Accumulating evidence suggest that chronotropic incompetence is not a factor limiting exercise capacity in the majority of HTx recipients and that HIT is a feasible, safe and effective way to improve exercise capacity and general health in stable, long term HTx recipients. This type of exercise should be introduced and used more frequently 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 basic research are needed to investigate these mechanisms. Future research is also needed to determine if the positive effects on CAV are reproducible, to examine which mechanisms cause these effects and to determine whether such an intervention has an effect on long term survival. The important question regarding optimal timing for introducing HIT after HTx also needs to be assessed. At present there is not (yet) sufficient evidence to conclude that HIT is superior to moderate exercise in HTx-recipients.

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