

Importance of physical capacity and the effects of exercise in heart transplant recipients

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Abstract

One of the most important prognostic factors in heart failure patients is physical capacity. Patients with very poor physical performance and otherwise eligible, may be listed as candidates for heart transplantation (HTx). After such surgery, life-long immunosuppression therapy is needed to prevent rejection of the new heart. The dark side of immunosuppression is the increased risk of infections, kidney failure, cancer and advanced atherosclerosis (cardiac allograft vasculopathy), with the two latter conditions as the main causes of later mortality. In a worldwide perspective, 50% of the HTx patients survive past 10 years. Poor aerobic capacity prior to graft deterioration is not only limited to the failing heart, but also caused by peripheral factors, such as limited function in the skeletal muscles and in the blood vessels walls. Exercise rehabilitation after HTx is of major importance in order to improve physical capacity and prognosis. Effects of high-intensity interval training (HIT) in HTx recipients is a growing field of research attracting worldwide focus and interest. Accumulating evidence has shown that HIT is safe and efficient in maintenance HTx recipients; with superior effects on physical capacity compared to conventional moderate exercise. This article generates further evidence to the field by summarizing results from a decade of research performed at our center supported by a broad, but not strict formal, literature review. In short, this article demonstrates a strong association between physical capacity measured after HTx and long-term survival. It describes the possible "HIT-effect" with increased levels of inflammatory mediators of angiogenesis. It also describes long-term effects of HIT; showing a positive effect in development of anxiety symptoms despite that the improved physical capacity was not sustained, due to downregulation of

exercise and intensity. Finally, our results are linked to the ongoing HITTS study, which investigates safety and efficiency of HIT in *de novo* HTx recipients. Together with previous results, this study may have the potential to change existing guidelines and contribute to a better prognosis for the HTx population as a whole.

Key words: High-intensity interval training; Peak oxygen uptake; Heart transplantation; Survival; Prognosis; Angiogenesis; Inflammation; Physical capacity; Exercise

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Core tip: Despite the positive effects of regular exercise after heart transplantation (HTx), HTx recipients' physical capacity remains subnormal, and a strong association between physical capacity and survival has been demonstrated. Thus, the positive effects of high-intensity interval training (HIT) are a growing field of research, attracting worldwide focus and interest. Although the "HIT-effect" is not fully understood, a possible contributing factor is the increased levels of inflammatory mediators of angiogenesis generated during exercise. More high-quality research is strongly warranted, but ongoing studies already have the potential to change existing guidelines and contribute to a better prognosis for the HTx population.

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INTRODUCTION

Heart transplantation

For patients with heart failure (HF) the 5-year mortality rates are 62% for women and 75% for men^[1], with even higher rates in patients with end-stage HF^[2]. Although these are old references, recent findings conclude that survival in HF patients has hardly changed since the 90's^[3]. Heart transplantation (HTx) is an established treatment to improve survival in selected patients with end-stage HF. From 1983 and to date, more than 920 HTx have been performed at Oslo University Hospital in Norway.

After HTx, the patients require lifelong immunosuppression to prevent rejection of the graft. These drugs have a potential to give adverse complications such as diabetes, gout, hypertension and osteoporosis, and serious side effects, such as higher risk of infections, renal failure and cancer. These side effects are the leading causes of death in the long-term, together with an advanced HTx-specific process of atherosclerosis, called coronary allograft vasculopathy

(CAV)^[4].

According to the 2012 ISHLT registry, the median survival for all HTx patients is 10 years, but if surviving the first year, the survival rates are higher and show a 63% survival past 10 years^[4]. Increased knowledge about CAV and immunosuppression has resulted in further improved survival. However, the HTx recipients still have a shorter estimated length of survival than the general population.

Physical capacity after HTx

The dynamics of physical capacity after HTx is illustrated in Figures 1 and 2. Physical capacity increases significantly after HTx as a result of therapy, as shown by peak oxygen uptake (VO_{2peak}) levels above 12 mL/kg per minute in published studies (Figures 1 and 2). Osada *et al*^[5] and these two figures show that the highest rate of increase is found within the first years. In nearly 70% of the studies, regardless of time after HTx, VO_{2peak} is below 20 mL/kg per minute, also classified as Weber function class B-C^[6]. Patients within function class B and C are shown to be similar to coronary artery disease (CAD) and HF patients referred to rehabilitation programs^[7]. VO_{2peak} is often used as the primary outcome measure in exercise intervention studies after HTx^[8].

Physical capacity as a prognostic variable

The gold standard measurement of physical capacity is VO_{2peak} , and is defined as "the maximum ability of the cardiovascular system to deliver oxygen to exercising muscles and of the exercising muscle to extract oxygen from the blood"^[9]. VO_{2peak} is shown to be a strong predictor of survival in general populations^[10,11], among patients with CAD^[12], and in patients with severe HF^[13]. Limited exercise capacity is the cardinal symptom in HF. The HF patients with $VO_{2peak} < 12$ mL/kg per minute are considered to have the worst prognosis, despite optimal medical therapy, and can be appropriate candidates listed for HTx^[14]. These patients are most likely men > 50 years of age^[4]. When evaluating younger patients and women, it is found reasonable to include age and gender adjusted levels of exercise capacity, and values $\leq 50\%$ percent of predicted VO_{2peak} differentiate better in these populations^[14].

However, studies addressing the relation between VO_{2peak} and survival after HTx are currently lacking, although a number of other predictors have been identified through register-data analyses. These predictors are: Non-ischemic cardiomyopathy as the primary diagnosis, younger recipient age, younger donor-graft age and shorter allograft ischemic time; all associated with a better long-term prognosis^[4,15,16]. The mortality beyond one-year after HTx has remained relatively constant, and Stehlik *et al*^[4] predict that interventions resulting in a reduction of mortal events in the long-term are needed to achieve further improvements in survival after HTx.

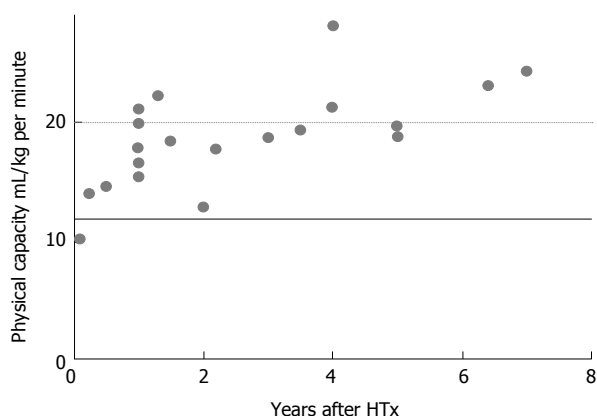


Figure 1 Physical capacity, as assessed by VO_{2peak} after heart transplantation from published studies, illustrated by years after surgery. Black line at 12 mL/kg per minute, show the threshold to be candidates for HTx, dotted line at 20 mL/min per kilogram, show the start of Weber function class A, representing good physical condition. The measurements are carried out from exercise tests from; Bernandi *et al.*^[65], Carter *et al.*^[66], Dall *et al.*^[65], Ewert *et al.*^[67], Givertz *et al.*^[68], Gullestad *et al.*^[69], Habedank *et al.*^[60], Haykowski *et al.*^[61], Hermann *et al.*^[66], Hognestad *et al.*^[62], Karpolat *et al.*^[63], Kavanagh *et al.*^[64], Kemp *et al.*^[65], Kobashigawa *et al.*^[66], Nytrøen *et al.*^[67], Osada *et al.*^[65], Renlund *et al.*^[67], Schwaiblmair *et al.*^[68], Squires *et al.*^[69], Tegtbur *et al.*^[100], Wu *et al.*^[77]. HTx: Heart transplantation.

In a recent retrospective study from our center, investigating survival in two different HTx populations ($n = 178$, $n = 133$), we found that VO_{2peak} and SF-36 physical function (PF) sum-score were strong predictors for survival in each population, respectively^[17]. In the “ VO_{2peak} cohort” ($n = 178$), the mean age was 52 years, mean age after HTx was 2.5 years, mean VO_{2peak} was 19.6 mL/kg per minute, 88% were men and mean observation time was 11 years. The most important predictors (analyzed by multiple Cox regression) for survival in this population were VO_{2peak} (HR = 0.917, $P < 0.001$) age at time of test (HR = 1.045, $P < 0.001$) and CAV development (HR = 1.968, $P = 0.001$), and the group above the median VO_{2peak} had an increased survival of four years. Similar results were found in the “SF-36 cohort” where the mean age was 54 years, mean time after HTx was 4.5 years, mean SF-36 physical function (PF) score was 90 and mean observation time was 10 years. The most important predictors (analyzed by multiple Cox regression) for survival in this population were the PF score (HR = 0.983, $P < 0.001$), age (HR = 1.077, $P < 0.001$), smoking history (HR = 1.077, $P = 0.016$) and CAV development (HR = 1.674, $P = 0.039$), and the group above the median PF score value had an increased survival of four years.

Other well-known predictors of HTx survival such as diagnosis prior to HTx, ischemic time, donor age, measurements of cardiac output and kidney function by creatinine did not add any additional explanation to the regression models.

The relationship between physical health and long-term survival

Earlier studies addressing survival, have estimated how

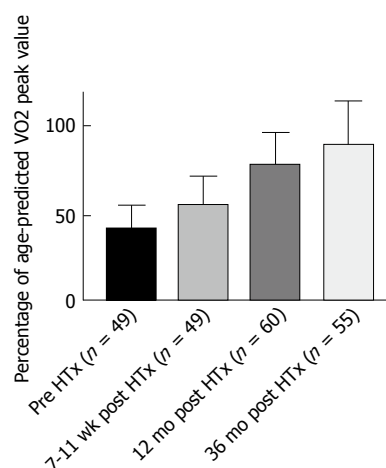


Figure 2 Illustration of the increase in peak VO_2 from pre heart transplantation to 36 mo post heart transplantation. The data presented in the figure is from the unpublished Schedule trial.

physical performance *pre* HTx is related to survival after HTx. Physical capacity (measured by VO_{2peak}) in this population is well known to predict survival and supports the clinicians in the selection of HTx candidates^[14]. Our study documented that also VO_{2peak} measured after HTx is a strong predictor for long-term survival^[17], and this result is in line with the only study we found that demonstrated a relationship between physical performance (measured by VE/ VCO_2 slope) and survival in a small sample of HTx patients ($n = 49$)^[18]. Other related studies on this topic describe how VO_{2peak} is related to soft end-points; how a beneficial VO_{2peak} correlates with NYHA class 1-2 after HTx^[19] and how the pre-transplant VO_{2peak} , together with age, predict the gain in physical capacity post HTx^[5]. Succeeding our study on survival, Rosenbaum *et al.*^[20] published new knowledge in this field, with a study investigating the effect of early rehabilitation on survival: They concluded that early cardiac rehabilitation participation after HTx could predict survival time.

The measurement of physical capacity requires CPET equipment and test personnel, and thus, is quite costly. Although VO_{2peak} is the gold standard to examine exercise performance, there are other physical tests with limited costs that can be useful in the follow-up, found to correlate with CPET results. Such physical tests are the 6-min walk test and the shuttle walking test^[21], but if these test are associated with prognosis remains to be determined. If resources are limited, we also found that the self-reported physical health (PF-score) showed a similar effect on long-term survival in the HTx population^[17]. Research in general populations underscore the importance of physical activity and report a dose-response effect on survival rates^[22,23], as well as a strong dose-response relation on self-reported health^[24]. As shown in another of our studies^[25], physical performance measured as VO_{2peak} is highly correlated with SF-36 PF sum-scores, and both were

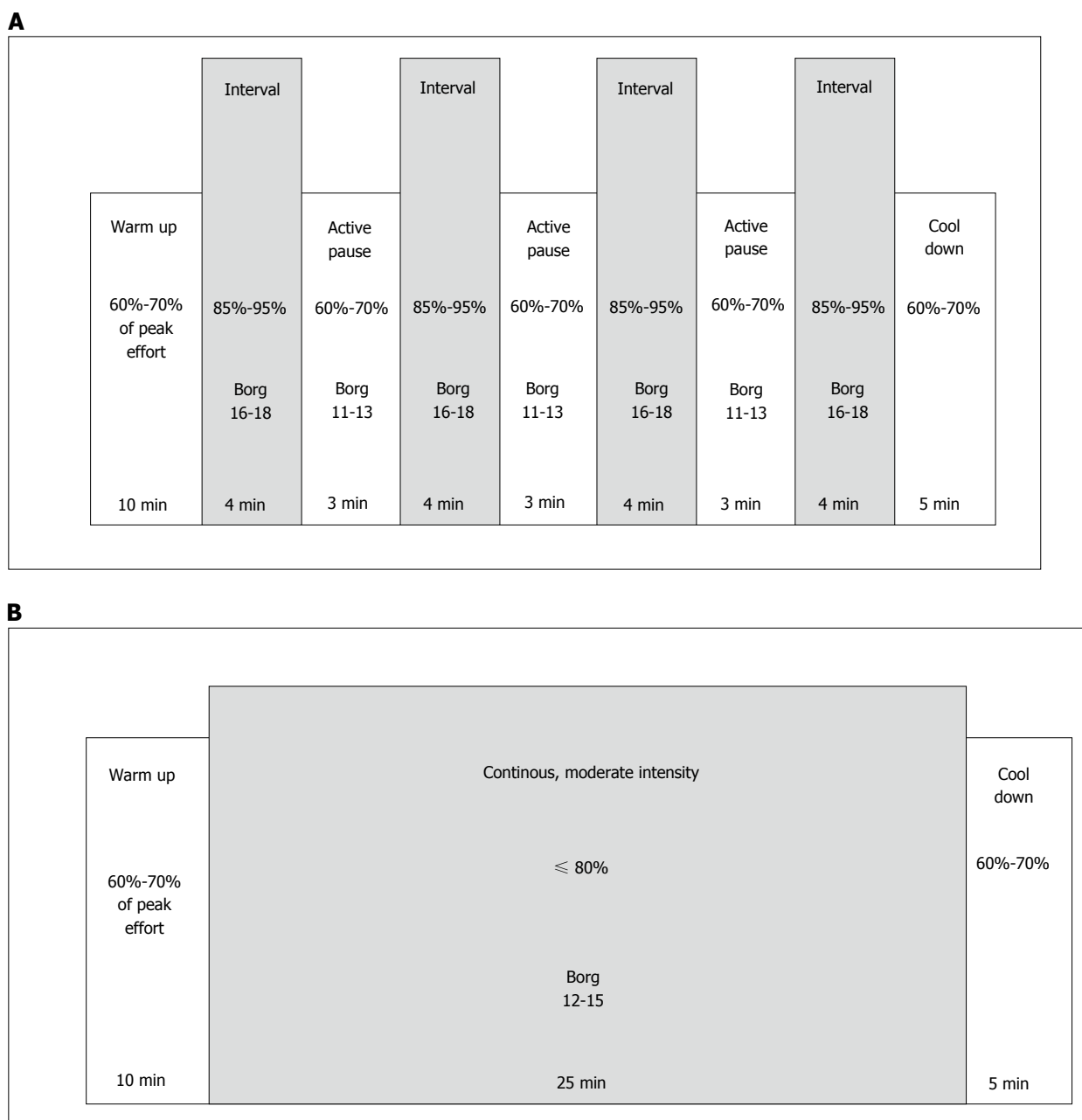


Figure 3 Illustration of two different exercise modalities. A: Illustration of a session with high-intensity interval training (HIT). HIT is an exercise strategy with alternating short periods of intense endurance exercise with less-intense recovery periods. A usual HIT session may include 4 × 4 min periods with high intensity (85%-95% of maximal capacity), with active recovery periods of 3min between each interval (with 60%-70% of maximal capacity); B: Illustration of a session with moderate intensity continuous training (MICT). MICT is an exercise strategy with moderate intensity (60%-70% of maximal capacity) of endurance exercise in periods for usually 25-30 min, with no recovery periods.

found to be highly associated with prognosis in our survival analysis^[17]. Accordingly, we suggest that such measures should be more frequently used after HTx to identify patients at higher risk for complications.

Exercise after HTx - the past and the future

To increase physical capacity and prevent long-term complications such as hypertension and diabetes, aerobic exercise after HTx has a positive effect, but HTx recipients' physical capacity still remains subnormal in most studies^[26]. High-intensity interval training (HIT) is proven to be a more efficient exercise modality

than moderate-intensity continuous training (MICT) in order to increase VO_{2peak}, shown in patients with HF^[27], CAD^[28], metabolic disease^[29], as well as in healthy individuals^[30]. The new knowledge has had a great impact on how general cardiac rehabilitation programs are organized today. These two different exercise modalities are illustrated in Figure 3. HIT corresponds to an intensity of 16-18 on Borg's rated perceived exertion (RPE) 6-20 scale^[31,32], and MICT to Borg 12-15.

Rehabilitation after HTx has traditionally had, and still has, a more conservative approach, with MICT as traditionally recommended, mainly due to uncertainty

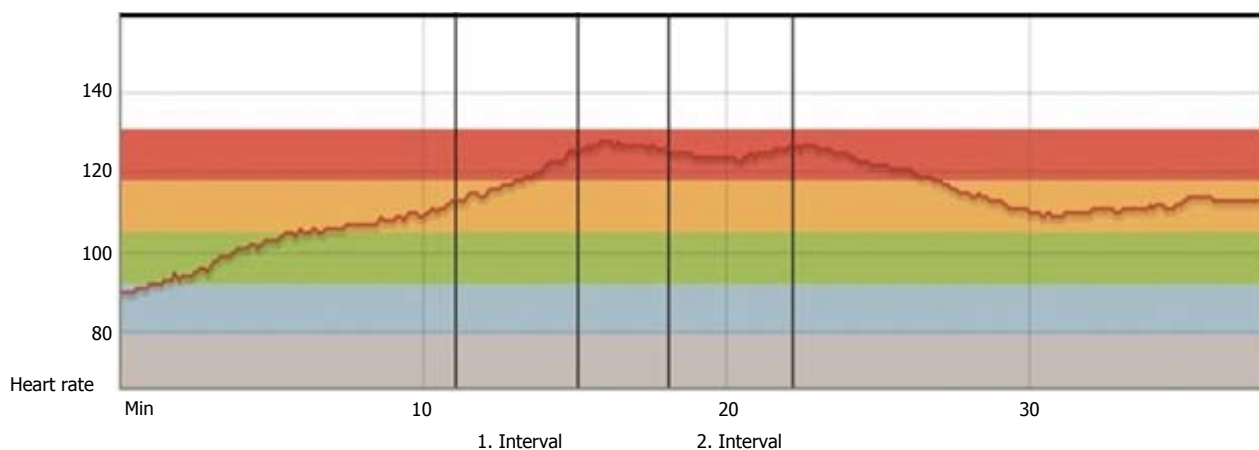


Figure 4 Heart rate during exercise 3 mo post heart transplantation. Patient from our hospital, 3 mo post-HTx: HR curve during warm-up, two high-intensity intervals divided by one recovery period and cool-down. The curve shows a typical pattern of impaired HR responses in the early stage after HTx. HTx: Heart transplantation.

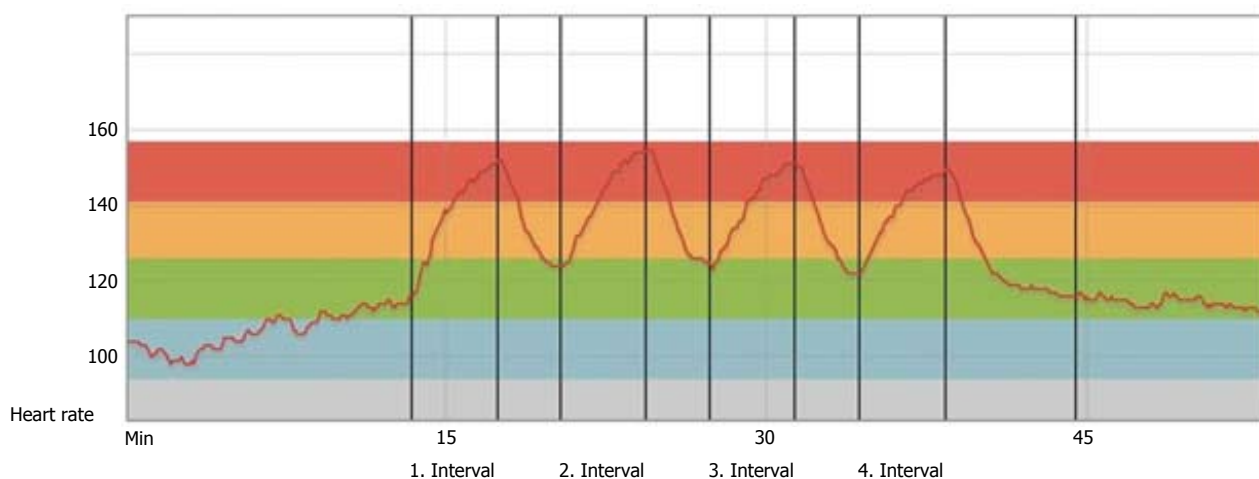


Figure 5 Heart rate during exercise 12 mo post heart transplantation. The same patient 12 mo post-HTx: Heart rate curve during warm-up four high-intensity intervals divided by 3 recovery periods and cool-down. The curve shows a largely normalized HR, with immediate HR adaptations to exercise intensity. HTx: Heart transplantation.

and concerns regarding denervation with consequently chronotropic incompetence and parasympathetic impairment^[33]. The heart rate (HR) will typically be higher at rest, with a slower increase during exercise, a lower maximum HR at peak exercise, and a slower HR decrease after exercise cessation (Figure 4).

The chronotropic incompetence is most prominent the first months after HTx and tends to be largely normalized in the majority of patients after 12 mo^[34], as illustrated in Figure 5. Recent randomized controlled trials (RCTs), have investigated the effect of HIT in maintenance HTx recipients and have to a large extent overruled the traditional, conservative approach with MICT^[35-37]. These studies showed that HIT increased VO_{2peak} significantly compared to the control groups, and that a HIT intervention was safe and well tolerated. References to some of these results are mentioned in the most recent recommendations for cardiac rehabilitation from 2013^[38]. The mechanisms of effect are probably multifactorial and might involve

improved chronotropic response (CRI)^[35,37], endothelial function^[36] and less development of CAV after a long-term exercise intervention^[39].

So far there are no studies on the effect of HIT in the novo patients, but a similar HIT intervention study is currently ongoing in Scandinavia^[40]. One of the goals in this study is to update, optimize and implement new exercise prescriptions also in this group.

Meta-analyses in HF populations^[41,42] find a possible long-term effect of exercise-based rehabilitation (MICT protocols) on survival and health related quality of life (HRQoL), and most importantly; a significantly decrease in re-hospitalization. Knowledge about exercise-based rehabilitation and the effect on mortality and hospital admissions in HTx recipients are currently missing, as recently stated in a 2017 Cochrane review on the effectiveness and safety of exercise-based rehabilitation in HTx recipients^[43]. The lack of research regarding possible long-term benefits of exercise was also pointed out in the published meeting report from

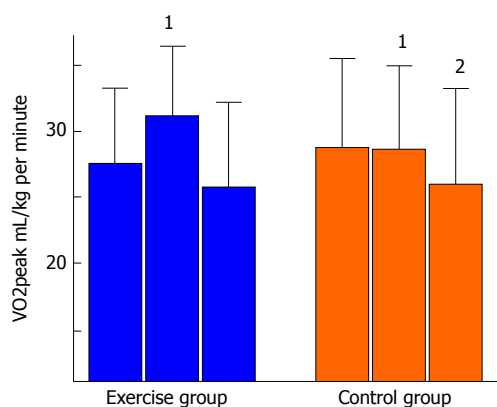


Figure 6 Measurements of VO_{2peak} at baseline, 1-year and 5-year follow-up. ¹Significant changes between groups; ²Significant changes from baseline to 5-year follow-up within group.

2014: "Consensus recommendations for a research agenda in exercise in solid organ transplantation"^[44].

HIT intervention and long-term effects

Regarding long-term effects of exercise in HTx recipients, we have conducted a 5-year follow-up study of a previous RCT investigating the effects of a HIT intervention^[25]. Forty-eight maintenance HTx patients, mean four years after HTx were randomized to HIT intervention or control with 12 mo duration^[37]. The study demonstrated a significant improved VO_{2peak} (mean difference between groups: 3.6 mL/kg per minute), increased muscular capacity and less development of CAV compared to the control group^[37,39]. However, at the 5-year follow-up ($n = 41$), the HIT group had not sustained the exercise intensity over time, and although the decline in VO_{2peak} from baseline to 5-year follow-up was numerically lower in the HIT-group, there were no significant differences between the groups for the parameters described above (Figure 6). These findings were explained by the similar amount of daily (moderate) activity in both the HIT and the control group, measured at the 5-year follow-up. Our results differ from a study by Moholdt *et al.*^[45] who investigated long-term effects of a HIT intervention after myocardial infarction (MI). These MI-patients still had a significantly higher aerobic performance at the 30 mo follow-up compared to the control group, explained by more frequent exercise in the HIT group. Although the initial 1-year gain in physical capacity in the HIT group was not sustained and the mean difference between groups at the 5-year follow-up was non-significant, only the control group had a significant decrease within group from baseline to the 5-year follow-up. This significant decrease, corresponding to a 9% decline in mL/kg per minute, could mostly be explained by an expected age-related decrease in VO_{2peak} . Healthy young adults show a decline of 3%-6% each decade, and this decline is shown to accelerate with age; a decline of 15% is found normal and corresponds to the age group of the TEX population^[46]. This age related

VO_{2peak} -decline is related to decreasing maximal stroke volume, decreasing blood flow to skeletal muscles and mitochondrial dysfunction^[47]. As for the HIT group, the decrease from baseline to the 5-year follow-up in VO_{2peak} was less pronounced (-6%), and could possibly indicate a hidden long-term effect of the intervention. In contrast, the development of anxiety symptoms was significantly different between the groups; the exercise group showed decreased symptoms of anxiety, whereas the control group had an increased anxiety symptom score. This beneficial trend in anxiety development together with no negative trends in other secondary end points, support the statements of HIT as a safe exercise modality in HF patients^[48], and in maintenance HTx patients^[35-37].

Nevertheless, more research is still needed regarding long-term effects of exercise, and to optimize the rehabilitation regimes and improve the HTx recipients' future prognosis^[43,44].

HIT intervention in de novo HTx recipients

While HIT already is an established exercise modality in patients with HF^[27] and CAD^[28], and more recently in maintenance HTx^[35-37], the upcoming results from the HITTS study^[40] will contribute to fill the gap of knowledge related to the effect of HIT among *de novo* HTx recipients. In addition to exercise capacity measurements, other important secondary outcomes are: development of CAV, improvements in chronotropic response and changes in cardiac and endothelial function. The results from the HITTS study will make a strong contribution to improve and increase the knowledge-base about how early HTx-rehabilitation should be organized in order to gain the most optimal results. The study is followed closely by our dedicated HTx-staffs in Scandinavia, and one of our main goals is to document knowledge about safety and effects of HIT, and thereby initiate an update of the current guidelines. If HIT is found to be safe (and with potentially beneficial effects) also among *de novo* HTx patients, the patients will have the possibility to participate in established cardiac rehabilitation programs, which usually combines both MICT and HIT exercise. These rehabilitation programs are usually group based, rather than only consistent individual physiotherapy, thus demanding less government resources.

Mechanisms behind the "HIT-effect"

As described previously, the effects of HIT interventions are so far mostly studied in healthy individuals, CAD and HF patients. The main mechanisms behind the increase in exercise capacity are shown to be through central factors, induced by a prominent improvement in cardiac output (CO)^[27,49]. However, the "HIT-effect" in maintenance HTx recipients show different results, seemingly with peripheral factors as the main mechanisms; by improvement in skeletal muscle exercise capacity^[37], endothelial function and

Table 1 A simplified illustration of the ANOVA results: The response in markers of inflammation and angiogenesis during high-intensity interval training and moderate intensity continuous training sessions

	MICT	HIT
General inflammation		
CRP	→	→
sTNFr-1	↑	↑
Vascular inflammation		
vWFd	↓	↑
VCAM	→	→
Blood platelets		
PDGF	↑	↑
sCD40L	↑	↑
DKK-1	↑	↑
Angiogenesis		
VEGF-1	↑	↑↑
Ang2	↑	↑↑
Tie-2	→	→
Endostatin	→	→
Cardiokine/myokine		
GDF-15	↑	↓ ¹
ST2	→	→
SPARC	↑	↑

¹The decrease is found in the recovery period (0-2 h) after the exercise-session. Horizontal arrows illustrate non-significant response during exercise. Arrows pointing up illustrate a significant increase with exercise, regardless of intensity, and two arrows illustrate a significant increase by increasing intensity (HIT). An arrow pointing down, illustrates a significant decrease in response during exercise. HIT: High-intensity interval training; MICT: Moderate intensity continuous training.

vasodilatation^[36], rather than an increased CO^[50]. The underlying triggers behind these peripheral effects are poorly understood, and the potential of inflammatory signaling pathways are not explored in detail. Markers of inflammation have been studied as an additional effect of exercise through long-term steady state levels (before and after exercise intervention), showing mostly neutral results^[36,39,51].

We hypothesized that investigation of immediate exercise effects in inflammatory signaling pathways during HIT could contribute to further explain the "HIT-effect" in the HTx recipients, and recently we performed such an exploratory study^[52]. Fourteen patients were included in the randomized cross-over study, comparing HIT to MICT. Blood samples were drawn before, during and after exercise. The main results from the enzyme immunoassays analyses were that exercise, regardless of intensity, induced a significant immediate response in several vascular, angiogenetic and particularly in platelet derived inflammatory mediators in HTx recipients shown in Table 1. HIT showed trends to induce an increased response in von willebrand factor (vWF), vascular endothelial growth factor 1 (VEGF-1) and Angiopoetin-2 (Ang-2), and a decreased response in growth derived factor 15 (GDF-15), compared to MICT (Table 1).

HIT and the immediate responses in markers of inflammation and angiogenesis

Exercise training, regardless of intensity, led to an

increase in multiple systemic, angiogenetic and platelet derived inflammatory mediators^[52]. These results are in line with published research showing the pro-coagulation state during exercise, with blood platelet activation potentially reflecting the increase in catecholamines and shear stress^[53], promotion of NO production from activated endothelial cells^[54,55], and regulation of the growth and repair of blood vessels^[56]. The activation of the endothelium and thereby induction of capillary growth in skeletal muscle through pro-angiogenetic mechanisms may play an important role in the beneficial effects of HIT. When we compared the response in inflammatory mediators during the HIT and MICT sessions, we observed a higher response in both Ang-2 and VEGF-1 with increased intensity. Kilian *et al.*^[57] have previously shown an increase in mRNA for VEGF in whole blood during HIT in healthy children. VEGF is dominantly secreted by working skeletal muscles, an essential factor to increase capillary density, oxygen delivery and thereby exercise performance^[58-60]. Based on our previous results showing improved muscular exercise capacity after HIT^[37], and now the finding of an increased VEGF response, we suggest that this mechanism is of high importance also in the HTx recipients. The fact that HIT markedly increased mediators of angiogenesis and neovascularization, may contribute to explain the different trigger mechanisms behind the two different exercise modalities.

CAV

CAV is characterized by intimal thickening and a more diffuse narrowing of the coronary arteries' lumen than conventional atherosclerosis^[61]. The mechanisms of development are described as both immunological and non-immunological, possibly modifiable factors^[62]. It can be detected by coronary angiography, but intravascular ultrasound (IVUS) is now more frequently used, and is a superior diagnostic tool to detect early changes in intimal thickening (early CAV)^[63]. The early CAV has been validated as a reliable surrogate marker for subsequent mortality, nonfatal major adverse cardiac events, and development of angiographic CAV following HTx^[64,65]. CAV progression is a highly prioritized field of research among HTx clinicians and researchers, to further improve HTx prognosis. As a result, Kobashigawa *et al.*^[66] introduced statin therapy that showed to have beneficial effects on one-year survival and the incidence of CAV. Statins became routine therapy after HTx at our center from 1997. More recently, a Scandinavian multicenter RCT (The Schedule-study) has shown that early everolimus initiation with calcineurin inhibitor withdrawal reduces the progression of CAV in *de-novo* HTx recipients^[67,68].

HIT and the effect on CAV

The effect of non-medical prevention strategies, such as HIT interventions, has also been studied by IVUS and have shown less progression of atherosclerosis both in mice^[69] and in patients after MI^[70]. We found

the same trend in maintenance HTx recipients after a HIT intervention^[39], but the positive effects were not sustained in the long-term as shown in the 5-year follow-up study^[25]. Furthermore, exercise is shown to have a positive influence on the endothelium through increased nitric oxide production, and by reduction of inflammation^[71,72]. This effect could possibly be enhanced through higher shear stress triggered with higher exercise intensity. A gain in endothelial function following a HIT intervention is found in CAD patients^[73]. However, a relatively small sample size in the 1- and 5-year follow-up studies^[25,39] limits our conclusion in the HTx population, and the effect of HIT on CAV should be examined in a larger sample and include a second intervention arm with MICT. It has been explored how early medical therapy can influence CAV progression in the long-term, and studies with everolimus are found to have positive impact on CAV severity in *de novo* HTx patients, whereas no effect is seen if everolimus is introduced later on^[74]. The effect on CAV severity by an early initiation was also sustained in the long-term^[67,68]. This illustrates an "opportunity window" during the first year after HTx. Knowing that the CAV development is most pronounced the first year after HTx, we anticipate that similar mechanisms may be seen with an early initiation of HIT. Results from the HITTS study^[40] will contribute to a better understanding of the relationship between exercise and CAV development.

Health related quality of life

The HRQoL after HTx has been reported to increase significantly, with high levels of satisfaction in overall HRQoL; also stable over a 5-year period (measured from 5 to 10 years after HTx)^[75]. Although, when HTx patients are compared with the general population, the HRQoL remains beneath normal values^[76]. To improve HRQoL, and especially physical health, exercise interventions have shown to be successful and this is in contrast to the more neutral results reported in control groups^[77,78]. Research on HRQoL after HTx regarding the effect of HIT (compared to MICT) is very limited, and the existing studies show mixed results; some studies show similar effects on HRQoL^[51], while we and others have shown a beneficial effect with a significant increase after HIT^[37,79].

Mental health, anxiety and depression

In the post-transplant stage the prevalence of significant depression and anxiety remains substantially above the general populations, and it tends to increase over time^[80,81]. As it is found that depressed HTx recipients have a higher risk of mortality, screening for depressive symptoms during follow-up is recommended^[81-83]. As an approach to increase mental health, the effect of exercise and HIT has been studied. The results showed that exercise decreases the burden of depression and anxiety, with HIT showing significant positive effects compared with usual care^[79]. Additionally, the results align with the correlation between higher physical

capacity and less depression and anxiety rates^[25,83,84].

In our 5-year follow-up study after a HIT intervention^[25], we measured physical and mental health as well as measures of physical capacity at each study visit, and at the 5-year follow-up there was significantly less development of anxiety symptoms in the HIT group compared to the control group. The long-term difference in anxiety between the HIT group and the control group is considered a valuable finding, as anxiety is a frequent health issue after HTx, especially in the long-term follow-up^[80]. Overall, there was a positive correlation between the measured VO₂ peak and the self-reported physical health (SF-36 PF sum-score). These findings might suggest that a 1-year "heavy" exercise intervention has a long-term value when it comes to self-confidence and trust regarding what your heart (and body) actually can tolerate of exertion, strain and physical work.

CONCLUDING REMARKS

Our findings, supported by a review of the existing literature, suggest that measures of physical health should be included frequently also after HTx, as they predict prognosis and survival in the long-term. A dose-response effect of physical capacity on survival was also found in the HTx population.

HIT is a feasible and efficient modality of exercise among maintenance HTx recipients, but the mechanisms behind this effect is poorly understood. Our results suggest that the beneficial effects seen in HTx recipients differ from CAD and HF patients, with more prominent peripheral effects from HIT exercise, rather than central adaptations with increased CO. We have showed that HIT significantly increased levels of inflammatory mediators of angiogenesis, suggesting that HIT can regulate and stimulate blood vessel formation in skeletal muscles and thus increase physical capacity.

Considering exercise prescription and future guidelines, our findings suggest that moderate levels of exercise and intensity are insufficient to maintain the improved VO_{2peak} achieved after a HIT intervention. Thus, intermittent periods of HIT are likely to be necessary. Also, the number and length of HIT intervals needed in a HIT session should be further investigated. If a modified HIT protocol with shorter and fewer intervals has comparable effect to a 4 × 4 protocol, it could probably increase the patients' motivation and adherence to exercise in the long-term. When considering other long-term effects, the benefit from a tough and intense HIT-intervention showed a positive effect on the development of anxiety symptoms. The exercise prescription in *de novo* HTx recipients is still conservative, consisting mainly of MICT exercise, but this traditional guideline might change when the ongoing HITTS study is completed. Existing gaps in knowledge are briefly mentioned in Table 2, and the results from the HITTS study will contribute to fill

Table 2 What is known and unknown in this field?

What is known in this field

A proper rehabilitation program including exercise training is recommended in all HTx patients

Good physical fitness is associated with improved outcome in HTx patients

The effect of HIT is superior to the effect of moderate training in general as well as for patients with coronary heart disease and heart failure

Accumulating evidence has shown that this is true also for HTx recipients 1-8 yr after HTx

Gaps in knowledge

There is no consensus on how, when and at which intensity exercise should be performed and organized after HTx

Because newly transplanted patients are totally denervated (without functional nerve supply resulting in impaired heart rate response), the effect of HIT has never been evaluated in this population, and the effect of HIT in *de-novo* HTx patients' needs to be investigated

The effect of HIT on late complications after HTx as CAV, diabetes mellitus, gout, renal function and graft survival needs to be explored

Data on whether a HIT intervention should be carried out decentralized or in cooperation with the primary health care services as well as the safety and cost-effectiveness are scarce

How to optimize ways to maintain exercise training during long-term follow up needs to be investigated

HIT: High-intensity interval training; HTx: Heart transplantation; CAV: Coronary allograft vasculopathy.

some of these gaps, and may also have the potential to update, optimize and possibly include HIT as a safe exercise modality in future guidelines.

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