

Pathophysiology of exercise capacity after heart transplantation

Kalp nakli sonrası egzersiz kapasitesinin patofizyolojisi

Melda Pelin Yargıç¹ , Zülfikare Işık Solak Görmüş² 

¹Sports Medicine Department, Meram Faculty of Medicine, Necmettin Erbakan University, Konya, Turkey

²Physiology Department, Meram Faculty of Medicine, Necmettin Erbakan University, Konya, Turkey

ABSTRACT

Heart transplantation is a life-saving treatment option for patients with end-stage heart failure. The improvement in exercise capacity of patients can vary to a great extent following transplant surgery. This review outlines the pathophysiology behind the changes in exercise capacity after heart transplantation. Reasons for exercise intolerance can be classified as central (cardiac) and peripheral (vascular and skeletal muscle). Cardiac mechanisms that limit exercise capacity are chronotropic incompetence due to denervation of the heart and diastolic dysfunction. Peripheral mechanisms are endothelial dysfunction and morphological alterations in the skeletal muscle. Some of the pathophysiological changes can be recovered with exercise therapy after the transplantation surgery. Research should be directed to reveal the safest and most effective exercise prescription to heart transplant recipients, targeting all of the mechanisms that contribute to exercise intolerance in a holistic approach.

Keywords: Heart transplantation, heart failure, exercise therapy, exercise tolerance

ÖZ

Kalp nakli, son dönem kalp yetmezliği olan hastalar için hayat kurtarıcı bir tedavi seçeneğidir. Nakil ameliyatından sonra hastaların egzersiz kapasitelerindeki iyileşmenin düzeyi büyük farklılıklar gösterebilir. Bu derleme, nakil sonrası egzersiz kapasitesinde görülen değişimin arkasındaki patofizyolojiyi özetlemektedir. Egzersiz intoleransının nedenleri santral (kardiyak) ve periferik (vasküler ve iskelet kası) olarak sınıflandırılabilir. Egzersiz kapasitesini sınırlayan kardiyak mekanizmalar, kalbin denervasyonuna bağlı gelişen kronotropik yetersizlik ve diyastolik disfonksiyondur. Periferik mekanizmalar ise endotel disfonksiyonu ve iskelet kasındaki morfolojik değişikliklerdir. Egzersiz tedavisi, kalp nakil alıcılarında bu mekanizmaların bir kısmını geri çevirebilmektedir. İlerleyen araştırmalar, bütüncül bir yaklaşımla egzersiz intoleransına katkıda bulunan tüm mekanizmaları hedef alan, kalp nakli alıcılarına en güvenli ve en etkili egzersiz reçetesini ortaya koymaya yönelik olmalıdır.

Anahtar Sözcükler: Kalp nakli, kalp yetersizliği, egzersiz tedavisi, egzersiz toleransı

INTRODUCTION

The world's first-ever human to human heart transplantation (H-tx) was performed by the team led by surgeon Christian Barnard in 1967, in Cape Town, South Africa. The patient survived for only 18 days after surgery and died of pneumonia with a fully functioning heart (1). Since that day, over 135,000 patients of all ages underwent heart transplantation. Heart transplantation is a life-saving treatment option for patients with end-stage heart failure, with a median survival of 10.7 years in adults and 16.1 years in pediatric recipients (2).

Life after heart transplantation surgery can take many different directions. At one end of the spectrum lies patients with half the VO_{2max} of healthy controls five years after transplant (3), whereas on the other end lie the patient who finished two Ironman Triathlons (3.8 km swim, 180 km bike, and 42.2 km run) within 14 weeks of each other, 28 months after transplantation surgery (4). There are many

influential anecdotes on patients who completed their first ever marathons after receiving a heart transplant (5,6).

Exercise capacity is a major determinant of quality of life in heart failure patients (7). This remains so even after heart transplant surgery, with lower readmission to hospital rates in patients who receive cardiac rehabilitation and improve their exercise tolerance (8,9). The purpose of this review is to outline the parameters that determine exercise tolerance after heart transplantation and the underlying pathophysiology.

CLINICAL and RESEARCH CONSEQUENCES

Chronotropic Incompetence and Diastolic Dysfunction

Autonomic nerves are cut during H-tx surgery, resulting in parasympathetic denervation and loss of sino-atrial node inhibition, leading to a persistent rise in resting heart rate

Received / Geliş: 08.01.2021 · Accepted / Kabul: 19.04.2021 · Published / Yayın Tarihi: 15.06.2021

Correspondence / Yazışma: Melda Pelin Yargıç · Necmettin Erbakan Üniversitesi Meram Tıp Fakültesi, Spor Hekimliği Anabilim Dalı, Konya, Turkey · meldapelin@gmail.com

Cite this article as: Yargıç MP, Solak Gormus ZI. Pathophysiology of exercise capacity after heart transplantation. *Turk J Sports Med.* 2021;56(4):203-8; <http://dx.doi.org/10.47447/tjism.0529>

(HR) (10). Due to the sympathetic denervation, exercise-induced augmentation in SA node activation is disrupted, leading to a decreased overall HR response during exercise, which is mostly based on circulating catecholamines (11). In addition to having an elevated resting HR and an inadequate rise in HR during exercise (lower HR reserve), these patients also reach maximal HR in the recovery period rather than at peak exercise. This may be attributed to the delay in catecholamine release (11).

Kao et al. presented critical findings regarding the maintenance of hemodynamics during exercise after H-tx surgery in their study and reported that transplant patients' stroke index (Stroke volume / Body surface area) remained lower than controls during exercise. Heart transplantation patients failed to increase their HR as high as healthy controls, despite having a 30% higher basal heart rate. As a result, H-tx patients had a 79% lower HR reserve (Maximal HR-Basal HR) compared to healthy controls. One of the mechanisms that leads to exercise intolerance in H-tx patients is failing to increase the HR as required during physical effort, namely the chronotropic incompetence (12).

Another mechanism to increase stroke volume, especially when failing to increase the HR, would be noted by applying the Frank-Starling law, which law suggests that ventricular output increases as preload (end-diastolic pressure) increases (13). The reason patients also failed to employ this mechanism was diastolic dysfunction (DD). Transplant patients had a consistently smaller end-diastolic volume index and similar end-systolic volume index and higher pulmonary capillary wedge pressure compared with normal during exercise (12).

DD is observed due to leukocyte-induced cytokines, myocyte loss and fibrous replacement resulting in an irreversibly progressive decrease in compliance at acute rejection (14). However, DD is not only evident in rejection cases. Significant complications can appear at different phases of transplantation and are due to causes as diverse as perioperative ischemia, reperfusion and hypertension (14). Besides, the use of cyclosporin may also induce myocardial fibrosis (15).

To summarize, H-Tx patients have a higher basal HR than controls, but they fail to increase it as much as hemodynamically necessary during effort because of the chronotropic incompetence. The potential compensatory mechanism to counter that would be the Frank-Starling mechanism. However, due to diastolic dysfunction, the stroke volume cannot be increased through the Frank-Starling mechanism either (12).

Cardiac Denervation and Reinnervation

Chronotropic incompetence as described previously is caused by heart denervation during transplantation surgery. Denervation was considered to be an irreversible consequence of transplantation until the beginning of the nineties (16-18). Later, phenomena such as improvement in heart response to exercise late after transplantation, the ability of some H-tx patients to experience ischemia-like chest pain, and the responsiveness of the transplanted heart to adrenergic drugs directed researchers to consider the possibility of post-transplantation cardiac reinnervation (19-21).

In 1993, Kaye et al. reported functional and neurochemical evidence of partial cardiac reinnervation after transplantation. Their study focused on sympathetic reinnervation and demonstrated the presence of noradrenaline release from the donor-heart in patients studied two years or after transplantation. In early cases (<18 months after H-tx), neurotransmitter release was not evident. Although neurotransmitter releasing capacity could restore itself to some degree, the capacity to recapture norepinephrine from the synaptic cleft remained significantly impaired (22).

Later in that decade, Bengel et al. confirmed that there is a very low likelihood of cardiac reinnervation in the first 18 months after surgery. Surprisingly they have reported that the process of reinnervation remains incomplete and continues for up to 15 years. The study also revealed the regionally heterogeneous nature of reinnervation, starting in the basal anterior region, then toward the apex, septal, and lateral wall, leaving the inferior wall denervated (19). The most important implication is that the reinnervation process remains incomplete.

A more recent study of Bengel investigated the effects of cardiac reinnervation on exercise performance and stated that along with an enhancement in the chronotropic response to exercise, an increase in the inotropic response resulted in vastly improved exercise capacity in the innervation group than in the denervation group. Presynaptic nerve terminals reappear in the myocardium as a result of sympathetic reinnervation, and local catecholamine uptake and storage are reestablished (23). The effects of reinnervation on global cardiac contractility tend to be marginal while the heart is at rest (24). However, during exercise, which stimulates the sympathetic system, reinnervation is necessary for an adequate contractile (inotropic) response (23).

The relation between sympathetic reinnervation and exercise capacity is two-sided. While exercise capacity is increased in patients with sympathetic reinnervation; the latter is more efficient in patients who undergo exercise therapy after heart transplantation. Training improves exercise capacity and the regulation of the autonomic nervous system

through the sympathetic nerves at both cardiac and vascular levels (25). Nevertheless, the most important determinants of sympathetic reinnervation are young age, fast and uncomplicated surgery, and low rejection frequency (20).

Reinnervation studies are mainly focused on the sympathetic system. The fact that the standard surgical technique applied during the years of pioneering reinnervation studies did not allow for parasympathetic reinnervation also played a role in this. However, with the development of the bicaval transplantation technique, parasympathetic reinnervation has begun to be investigated (26). Parasympathetic reinnervation is particularly important as the effectiveness of baroreflex-mediated blood pressure control is largely based on rapid responses in the heart rate mediated by the vagus. As a result, when only sympathetic reinnervation occurs, a low heart rate variability is observed, resulting in insufficient control of baroreflex-mediated blood pressure (26). Another importance of preservation of the parasympathetic innervation is the cardioprotective effects of parasympathetic tone (27). Parasympathetic reinnervation is possible and depends on the type of surgery. Resecting the recipient aorta extensively or totally results in better chances of parasympathetic reinnervation, allowing a better adaptation to physical exercise through an increase in control of blood pressure by larger reflex changes in heart rate (26).

In short, cardiac reinnervation occurs in some patients, starting after 18 months and continues up to 15 years post-surgery. Sympathetic reinnervation is critical for a better chronotropic and inotropic response to exercise, whereas parasympathetic reinnervation is important for baroreflex-mediated blood pressure control.

Changes in Peak Oxygen Uptake

Many studies investigated the changes in VO_2peak following heart transplantation. Gullestad et al. studied 174 patients 3.5 years after the operation and reported a mean VO_2peak of 19.4 ± 0.4 ml/min/kg, which accounts for 70% of the age-predicted value (28).

Osada et al. also reported that in 56 heart transplant recipients three had 70% ($\pm 17\%$) of their age-predicted VO_2peak three years after surgery (29). Several researchers reported much lower values, such as 51% of age predicted VO_2peak ($n=47$), whereas others reported 101% of age-predicted values ($n=7$) (3,30).

Although higher and lower values have also been reported, in most studies the peak oxygen uptake (VO_2peak) levels vary between 50% to 70% of the general population and a decreased VO_2peak level predicts poor prognosis (31,32).

Exercise therapy improves VO_2peak in heart transplant recipients and the mean improvement is between 1.3-5.6 ml/min/kg (31). Different exercise protocols result in different levels of VO_2peak improvement. In the study of Hermann et al., eight weeks of high-intensity interval training improved VO_2peak by 5.6 ml/min/kg comparing with controls (33), whereas Tegtbur et al. reported that a one-year home-based ergometer-training program (intensity at 10% below anaerobic threshold) improved the VO_2peak by only 1.3 ml/min/kg (34).

Skeletal Muscle Wasting and Atrophy

Heart transplantation candidates suffer from end-stage heart failure and live with very limited exercise and functional capacities. At the time they receive a new heart, their exercise capacity and daily physical activity level would have been very restricted for a long time. Therefore, the typical effects of detraining are observed among heart failure patients' skeletal muscle biopsies. These alterations include a decrease in mitochondria volume, capillary density, type 1 fiber rate and oxidative enzyme capacity and overall demonstrate a reduced oxidative capacity of working muscle (35).

Skeletal muscle biopsies performed before and at 3 and 12 months after cardiac transplantation revealed that skeletal muscle enzyme activities of phosphofructokinase, citrate synthase, and beta-hydroxyacyl coenzyme A dehydrogenase significantly increase after H-tx. Also, fiber cross-sectional areas display a significant increase 12 months after cardiac transplantation, albeit preserving the type 2 fiber dominance and remaining lower than controls (36). One morphologic characteristic that does not improve after surgery is the capillary density, namely the number of capillaries surrounding each fiber. Capillary density remains as it was before H-tx even 12 months after surgery (36,37). Besides physical inactivity due to restricted exercise capacity, corticosteroid and cyclosporin treatments may contribute to the deterioration of the skeletal muscle in H-tx patients as well (38).

Considering that skeletal muscle is a large tissue that consumes most of the oxygen during exercise, changes in skeletal muscle morphology can have a profound impact on the exercise ability of patients. Indeed, routine home exercise therapy has gradually increased exercise capacity over 12 months of training, suggesting that exercise treatment may mitigate the adverse side effects of immunosuppressive therapy on skeletal muscles. The authors of the report proposed that, even late after H-tx, exercise training should be undertaken consistently to avoid an increased reduction in cardiovascular ability and skeletal muscle function (34).

There is no longer any doubt about the positive effects of exercise therapy, and recently more researches have focused on finding the most effective exercise modality. Studies are suggesting that high-intensity interval training (HIIT) exercises may be more effective than traditional moderate-intensity exercise prescriptions. A study showed that HIIT had a superior effect on oxygen uptake and led to an unexpected increase in peak HR accompanied by a faster HR recovery compared to continued moderate exercise. This result indicates that HIIT improves the chronotropic response better than continuous moderate exercise (39). There are a limited number of studies that compare the effects of HIIT to moderate-intensity exercise. Instead, most compare HIIT to no-exercise interventions (40). With our current knowledge, HIIT appears to be a candidate for routine practice as a safe exercise option in H-tx patients. However, more research is needed to demonstrate the advantages of HIIT to moderate-intensity exercise.

Frailty

Frailty is characterized as an increased vulnerability and decrease in functionality across multiple systems (41). The phenotype of frailty refers to slow walking speed, weakness, weight loss, physical inactivity, and exhaustion. One pathway leading toward the frailty phenotype is age-associated, and it leads to sarcopenia as a result of inflammation and a decline in androgen hormones. Another pathway that leads to frailty stems from cardiovascular disease and subclinical impairments resulting from it, genetic predispositions, and decreased resiliency to stressors (41). Although primary (age-associated) and secondary (cardiovascular disease-related) frailty have subtle differences, the two entities are most likely not mutually exclusive.

Frailty is linked to poor outcomes in chronic heart disease patients and heart transplant candidates and recipients (41). Frailty within six months of HTx is linked to an increased risk of death and extended hospitalization following transplantation. Psoas muscle volume before transplantation is also negatively correlated with duration of hospitalization after transplantation (42).

Endothelial Dysfunction

A healthy endothelium establishes the equilibrium between vasodilating vs. vasoconstricting, inflammatory vs. anti-inflammatory, and thrombotic vs. anti-thrombotic factors. In endothelial dysfunction, the scale tips towards a vasoconstrictive, inflammatory, and thrombotic phenotype (43).

The pathophysiology of heart failure with preserved ejection fraction, a subgroup of heart failure, sheds light on the importance of the endothelium function in exercise capacity. The most prominent feature of heart failure with pre-

served ejection fraction is exercise intolerance, pointing out the importance of peripheral mechanisms underlying the reduced functional capacity and exercise tolerance. Even in the absence of favorable central hemodynamic activity, physical training can improve the exercise capacity through peripheral adaptive mechanisms in heart failure (44). One of these peripheral mechanisms is skeletal muscle adaptation as mentioned earlier. Another important peripheral mechanism is the restoration of endothelial function. On the other hand, an improved vascular function also means improved oxygen delivery to skeletal muscle (45). Therefore, the two peripheral mechanisms that contribute to improvements in exercise capacity should not be considered separately, rather they interact with each other closely.

Endothelial dysfunction in H-tx patients presents clinically with 50% higher systemic vascular resistance during exercise compared to healthy controls (12). As Andreassen et al. demonstrated in their study, exercise capacity in H-tx patients tends to be closely correlated with attenuated endothelium-dependent vasodilation in peripheral microcirculation (46).

A way to measure the endothelial function is by assessing the endothelium-dependent, flow-mediated dilation (FMD) via brachial artery ultrasound (47). Research performed using this approach revealed that endothelial dysfunction is evident in patients with heart failure, regardless of etiology. However, whether the endothelial function will be restored after cardiac transplantation depends on the etiology of heart failure. Patients without ischemic heart disease have more favorable outcomes in regard to correcting peripheral endothelial function, than patients with prior atherosclerotic coronary disease (48).

Immunosuppressive therapies adversely affect the vasculature as well, besides their previously mentioned adverse effects on diastolic dysfunction and skeletal muscle wasting. Although both the commonly used tacrolimus and cyclosporine agents contribute to vasculopathy, the former is reported to be less toxic in terms of microvascular endothelial function, intimal thickening, and vascular remodeling (49).

The endothelium benefits from exercise therapy through correction of comorbidities, upregulating and phosphorylating eNOS through increased shear stress and vascular endothelial growth factor 2 release, and leading to an increase in NO bioavailability (50), reducing oxidative stress by downregulating angiotensin receptors and nicotinamide adenine dinucleotide phosphate oxidase (51), increasing the number of circulating angiogenic T lymphocytes which control the mobilization of endothelium-repairing endothelial progenitor cells from the bone marrow (52). However,

there are reports in the literature indicating that exercise training has no effect on vascular function in H-tx recipients, as well as reports that demonstrate improved vascular function after training (38). The effectiveness of exercise therapy on endothelial dysfunction of H-tx patients needs further investigation.

In summary, the presence of endothelial dysfunction is dependent on the etiology of heart failure, and the extent of dysfunction varies according to the immunosuppressive agent. Failure to adequately dilate the vasculature leads to decreased oxygen supply to skeletal muscle, impairing exercise capacity.

Psychological and Psychosocial Factors

Being a heart transplant recipient is a very important life event. It not only affects the physiology of the patients, but also changes the mood and psychology (53). The most common mood disorder developing in heart recipients prospectively followed during the first two years after transplantation is major depression. Although not that prevalent, post-traumatic stress disorder was also observed among transplant recipients (54). Following HTx, higher levels of psychological distress, such as anxiety and depression, have been linked to lower aerobic capacity (55). Psychosocial factors are important determinants of exercise therapy response as well. It was reported that an eight-week home-based therapy failed to improve the quality of life, anxiety and depression scores of heart transplant patients, whereas the hospital-based, supervised exercise therapy successfully improved all the above mentioned parameters, as well as peak VO_2 (56).

CONCLUSION

In conclusion, both central (cardiac) and peripheral (vascular and skeletal muscle) mechanisms contribute to impaired exercise capacity after cardiac transplantation. Heart denervation causes chronotropic incompetence (a decrease in HR reserve) and can be restored to some extent by sympathetic and parasympathetic reinnervation. Diastolic dysfunction is another central mechanism that causes less end-diastolic volume and impairs inotropy. Peripheral mechanisms include endothelial dysfunction and alterations in skeletal muscle morphology. Changes in skeletal muscle can be reversed by exercise training to some degree, but the reversing effects of physical training on endothelial dysfunction are not as clear.

Research should be directed to revealing the safest and most effective exercise prescription for heart transplant recipients. The most effective exercise therapy would be the one that targets improving all underlying mechanisms,

both central and peripheral, contributing to exercise intolerance in a holistic approach.

Conflict of Interest / Çıkar Çatışması

The authors declared no conflicts of interest with respect to authorship and/or publication of the article.

Financial Disclosure / Finansal Destek

The authors received no financial support for the research and/or publication of this article.

Author Contributions / Yazar Katkıları

Concept - M.P.Y., Z.I.S.G.; Design - M.P.Y., Z.I.S.G.; Supervision - M.P.Y., Z.I.S.G.; Literature Review - M.P.Y., Z.I.S.G.; Writing Manuscript - M.P.Y., Z.I.S.G.; Critical Reviews - M.P.Y., Z.I.S.G.

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