# 4

# Physical Rehabilitation

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## 1. Introduction

Heart transplantation is the ultimate therapy for patients in the end stage of heart failure in order to either restore or promote patients a better functional performance (Bocchi, 2001; Guimarães, 1999).

The first heart transplant in the world was performed in 1967 and the procedure has been even more present in this area since then (Kaye, 1993). Several clinical efforts and advances were seen in the last decade in this field, with the incorporation of new surgical techniques, new immunosuppressive drugs, new diagnostic methods and approaches in the early and late postoperative. All advances were able to contribute to greater functional status and less impairment or co-morbidities.

Many different centers around in the world perform heart transplantation and, thus, are able to contribute to favorable results in terms of survival and quality of life on heart transplant recipients (Bocchi, 1999).

The practice of regular physical activity has been recommended for rehabilitation after cardiac transplantation in order to reduce and control co-morbidities (such as hypertension, diabetes, vascular disorders, mainly developed due to continuous use of immunosuppressive drugs), as well as to restore physical capacity and daily activities (Guimarães, 1999).

Nevertheless, crucial attention is needed when prescribing a physical activity program heading for heart transplant recipients, because they remain with some impairment previously to the surgery, and gain some other disabilities due to the transplantation procedure itself and due to the use of required drugs to control organ rejection.

## 2. Prevalence

Heart failure (HF) is the final common pathway of most diseases which affect the heart, and it is performed in these patients because of the severity and urgency of their disease (Reemtsma, 1985). Thus, **heart transplant**, or a **cardiac transplantation**, is a surgical transplant procedure performed on these patients and it is recognized as the gold standard therapy for patients facing the end stage of heart failure because there is an increased worsening imbalance between the demand for transplants and the supply of the organs in HF (Haywood, 1996).

The surgical procedure takes a working heart from a recently deceased organ donor (an allograft) and implants it into the patient (called recipient). The patient's own heart may either be removed (orthotopic transplant) or, less commonly, left in to support the donor heart (heterotopic transplant);

The cardiac transplantation contributes to a low operative mortality but an undesirable high postoperative mortality. This elucidates the fact that heart failure and the surgery represent some important current clinical challenges in healthcare and an epidemic in progress (Guimarães, 2004).

Whenever there is a careful selection for choosing the donor and recipient, there is also a significant increase in survival, exercise capacity, on return to work and quality of life of this group of patients (Banner, 1989).

From the early 80's, almost 10% of people died on the waiting list for cardiac transplantation, mostly due to sudden cardiac deaths, and the average length of time patients wait before undergoing transplantation is increasing each decade (Haywood, 1996) maybe because of the increase number of patients suffering from HF and the improvement of its palliative treatment (Guimarães, 2004).

Heart transplantation has evolved and long term survival is expected for most heart transplant recipient because of the improvements in organ preservation, surgery and immunosuppressive drug management, and physical rehabilitation.

## 3. Pathophysiology

In general, heart transplant surgery has become an effective therapeutic option in the management of end stage heart disease because it is able to restore physical function because the new heart doesn't have the limitations the old heart had.

There is an association of better left ventricular function one year after cardiac transplant operation with donor-related factors (donor age and sex, ischemia time), and with recipient-related factors (recipient age and sex, frequency of acute rejection), type of immunosuppressant drug, and frequency of hypertension (Reid, 1988).

However, the procedure itself promotes complete organ denervation by the postganglionic neural axons section. During heart transplant surgery, the atria of both, the giver and the receiver are sutured together (el-Gamel, 1998). The original sinoatrial node remains innervated, the vagus nerve is severed during the operation, but the electrical impulses generated by it cannot cross over the suture line.

Because the sinoatrial node of the transplanted heart, which determines heart rate (HR) is totally denervated, this neural section may be responsible for either a delay or an unsatisfactory autonomic response (Guimarães, 1999), which will depend mostly on circulating catecholamines to stimulate the heart (Kaye, 1977) unless nerve regrowth occurs.

Therefore, the absence of afferent neural control of heart rate leaves the heart under the influence of hormones in addition to internal control. The lack of neural signals to the sinoatrial node is indicated by the reduced maximal HR, heart rate variability, as well as changes in the HR response during exercise (Di Rienzo, 2001) and during change of posture (Doering, 1996).

The surgery in these patients promotes inefficient control of heart rate (Kaye, 1977) usually with a high resting HR and a small increase in HR in the first minutes of exercise. Perhaps maximal HR is reached in the recovery period of exercise, and not at peak exercise, taking longer to return to baseline (Guimarães, 1999), as previous shown in Fig. 1.

However, the vasomotor control (neural and hormonal) is not affected by surgery. The changes in this system may appear due to adaptive mechanisms to drug therapy (Toledo, 2002).

Initially it was thought that the denervation was permanent, and there was only the dependence on circulating catecholamines to achieve maximal heart inotropic and chronotropic stimulation (Kaye, 1977). As time passed by and recent studies have been performed, it has been shown that there is a reinnervation process over time after surgery (Fuentes, 2010), because significant higher $VO_2$, AT (anaerobic threshold), VE (Schwaiblmair, 1999), myocardial function and coronary artery tone are shown after this surgery (Burke, 1995). reinnervation happens in an heterogeneous pattern (Wilson, 1993).

It is known that time after transplantation is recognized as a significant factor correlated to partial autonomic reinnervation among these recipients (Schwaiblmair, 1999). In the majority of recipients with more than one year after cardiac transplantation, cardiac norepinephrine reapers. This support the presence of late heterogeneous sympathetic reinnervation (Wilson, 1993).

Data from Heart Failure Clinics of Heart Institute compare the $O_2$ consumption increase to the heart rate increase during exercise. It shows that a cardiac transplant recipient at short-term transplantation have the increase of $VO_2$ during cardiopulmonary exercise test not matched to the increase in HR (Figure 1). The same patient at long-term transplantation showed a closer relationship to this increase (Figure 2), so this might corroborate the idea of partial reinnervation described over time.

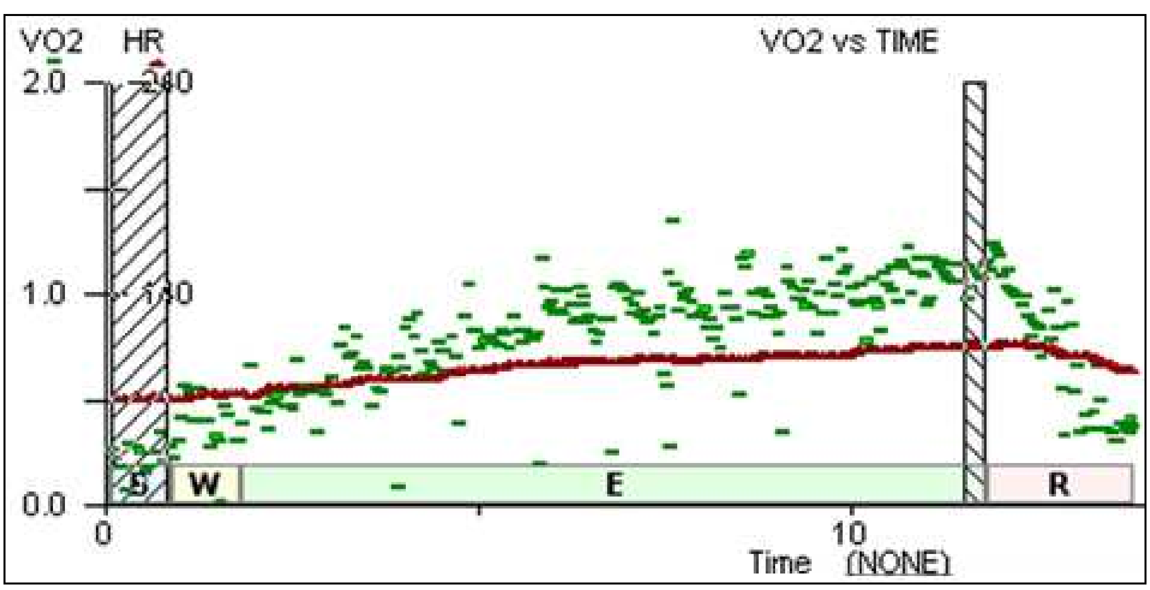


Fig. 1. Response in recent (5 month) post transplant recipients. HR in red, $VO_2$ in green.

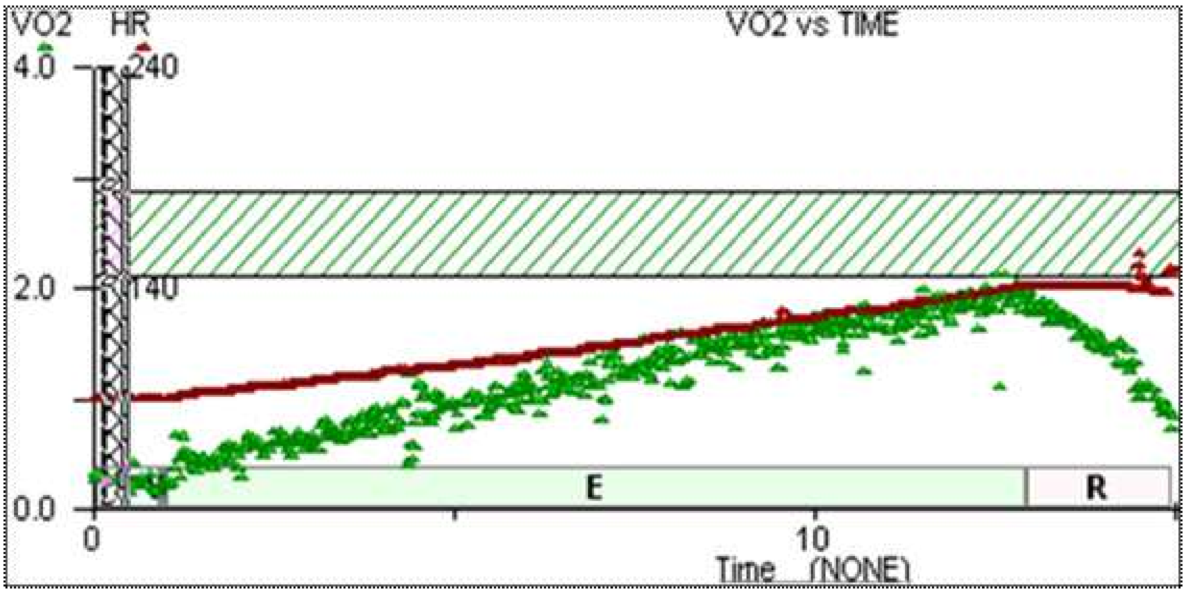


Fig. 2. Response in late (9 year) post transplant recipients. HR in red, $VO_2$ in green.

Thus, heart rate control acts different from healthy subjects. It becomes more elevated at rest; nevertheless, during exercise, there is gradual delay of its increase from the exercise start to the peak HR. As a result, by the time heart transplant recipients reach their peak HR, it is, indeed, lower than peak HR in healthy subjects. Then, HR decreases in a slow way during the recovery period (Guimarães, 1999). This described finding in exercise could be identified in one of the patient referred to Heart Failure Clinics of Heart Institute, in Brazil (Figure. 3).

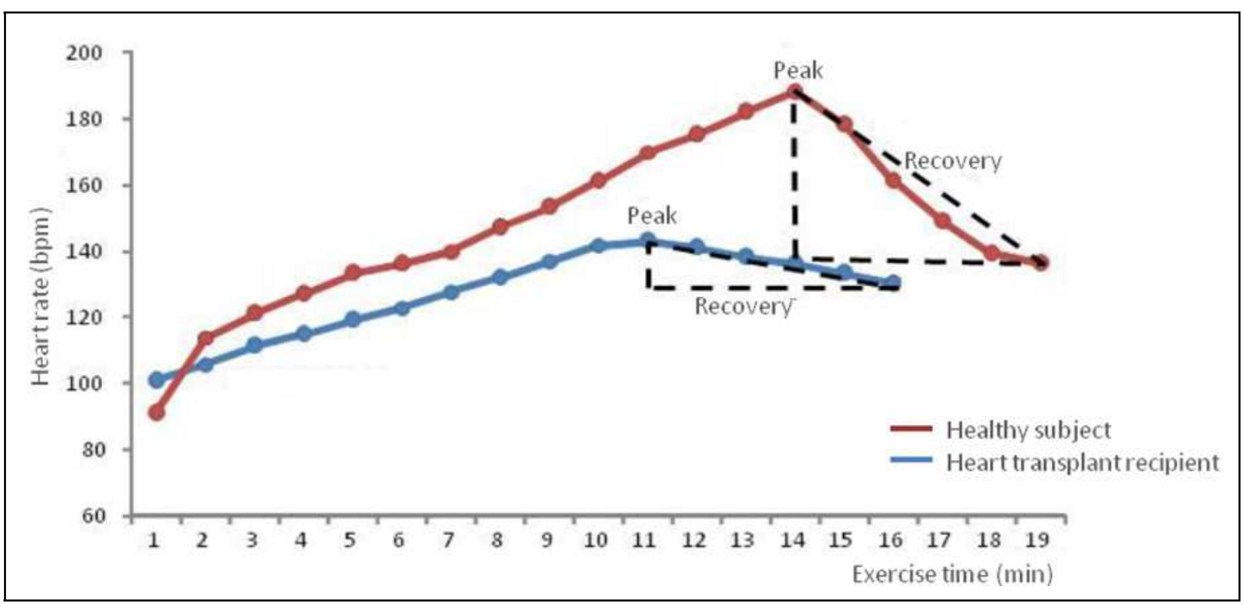


Fig. 3. Heart rate(HR) representation in a sedentary healthy subject (in red) and in a sedentary heart transplantation recipient (in blue).

Comparing the same data from heart transplant recipients and heart failure patients from Heart Failure Clinics of Heart Institute, both, resting HR and peak HR, after surgery becomes significantly higher compared to the same data from healthy subjects, although there is no change in their HR reserve (Figure 4).

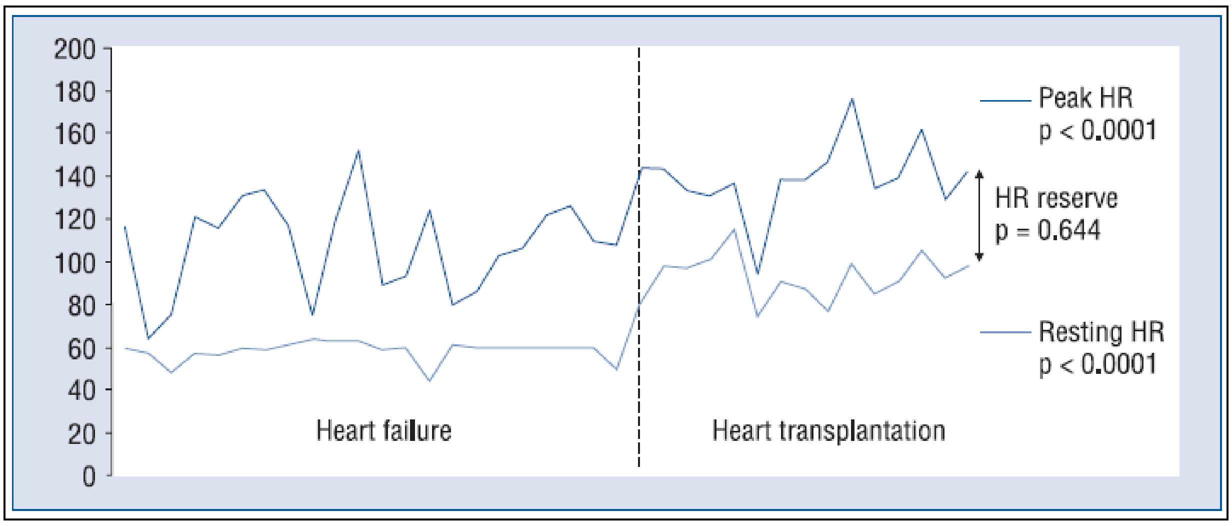


Fig. 4. Resting heart rate, peak heart rate and heart rate reserve in heart failure patients and heart transplant recipients ; HR — heart rate.

Peak heart rate (percentage of the maximum predicted for age) is significant higher in heart transplant recipients than in heart failure patients (Carvalho, 2009a) because the heart remains partially denervated, as it is shown in Figure 5. Thus, the general use of maximum HR adjusted for age recommended by the Task Force, 2006, known as 220 – age, cannot be applied to transplant recipients in order to identify their maximum effort and to prescribe exercise (Casadei, 1992; Guimarães, 2010).

Indeed, no patient reached the maximum heart rate predicted for their age during a treadmill cardiopulmonary exercise test. A heart rate increase in heart transplant patients during cardiopulmonary exercise test comes around 80% of the maximum age-adjusted value (Carvalho, 2009a).

Masked mechanisms responsible for the increase of cardiac output in these patients have close correlation to reaching their physical capacity (Casadei, 1992). In fact, heart transplant recipient's norepinephrine plasma level is lower, at rest, than either healthy or heart failure subjects. But it becomes twice higher than healthy subjects do, after the 6-minute walking test (Guimarães, 2010).

Increases in heart rate and stroke volume at exercise are first linked to the augmented venous return, and later to the increased plasmatic noradrenaline level. Hence, reduced cardiac output response to exercise results in early anaerobic metabolism, acidosis, hyperventilation and diminished physical capacity.

Peak oxygen consumption is reduced in transplant recipients compared to healthy subjects, which may be related to the existence of remaining systolic and diastolic dysfunction (Patel, 2003), muscular atrophy and hormonal abnormalities due to heart failure persistence after transplantation (Gryglewski, 2001), in addition to the use immunosuppressive drugs that reduce exercise capacity, and sympathetic stimulation (Banner, 1989).

A strong relationship was found between percentage of heart rate reserve (%HRR) and percentage of oxygen consumption reserve (%$VO_2$R) in heart transplant during cardiopulmonary exercise test, as it follows in Figure 6 (r=0.95, p<0.0001). The %HRR–%$VO_2$R linear regression between 0 intercept and 1 intercept between the slope of each

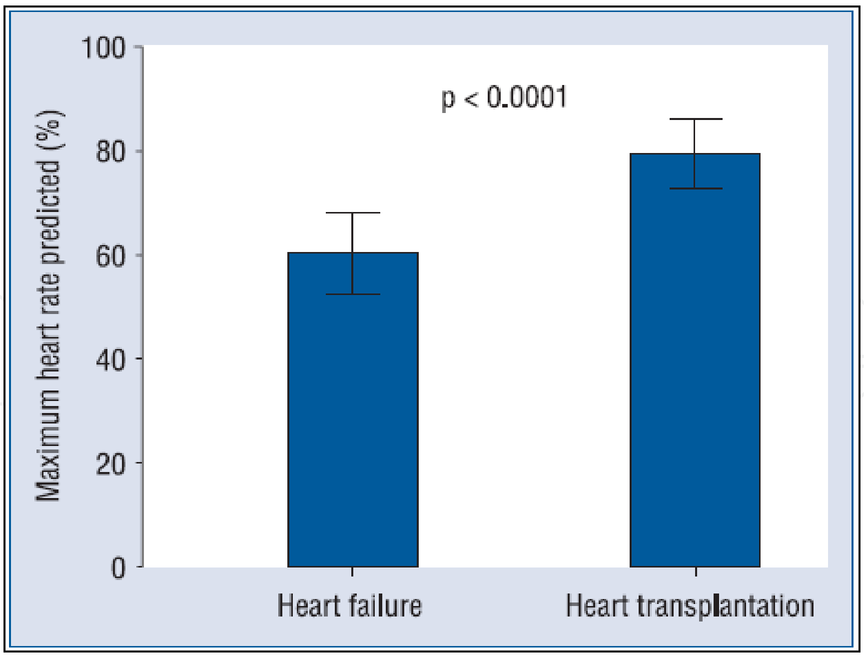


Fig. 5. Mean peak heart rate (percentage of the maximum heart rate predicted for age) in heart failure patients and in heart transplantation recipients. Data is presented as the mean ± 95% confidence interval.

patient showed a slope of −0.23, which means that it is far from the perfection expressed by a slope of 1. Perhaps different terms of heart transplantation and, consequently, different reinnervation status patients could have influenced the imperfect reliability of the %HRR versus $\%VO_2R$ (Carvalho, 2009b).

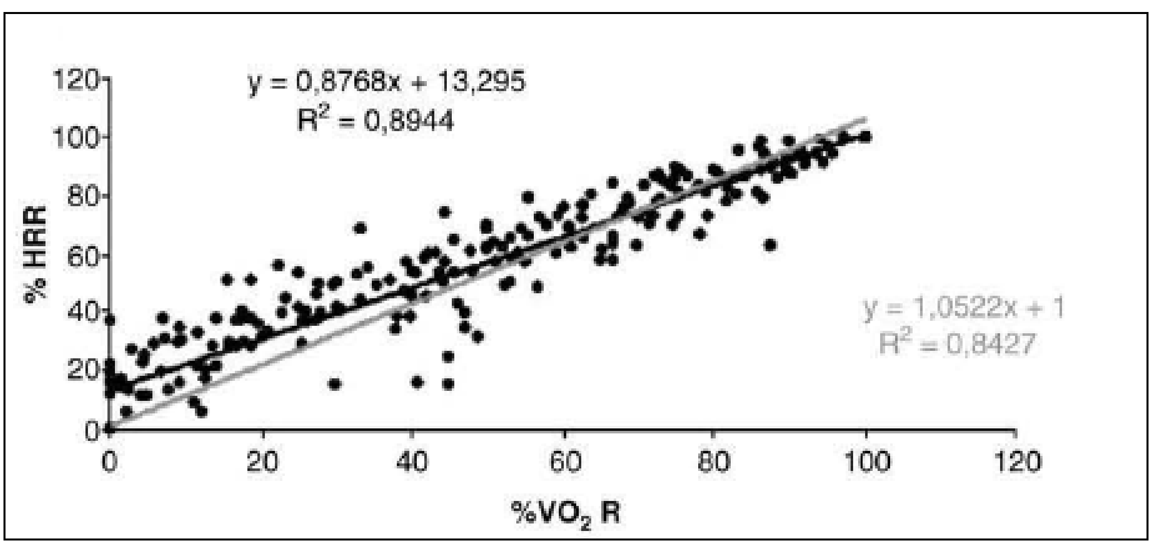


Fig. 6. Percentage of heart rate reserve (%HRR) and percentage of oxygen consumption reserve ($\%VO_2R$)

A close relationship was also found between %peak heart rate versus %peakVO2 ($r=0.91$, $p<0.0001$) and absolute heart rate versus absolute $VO_2$ ($r=0.67$, $p<0.0001$). They are expressed in both, Figure 7 and Figure 8, data extracted from Heart Failure Clinics of Heart Institute (Carvalho, 2009b).

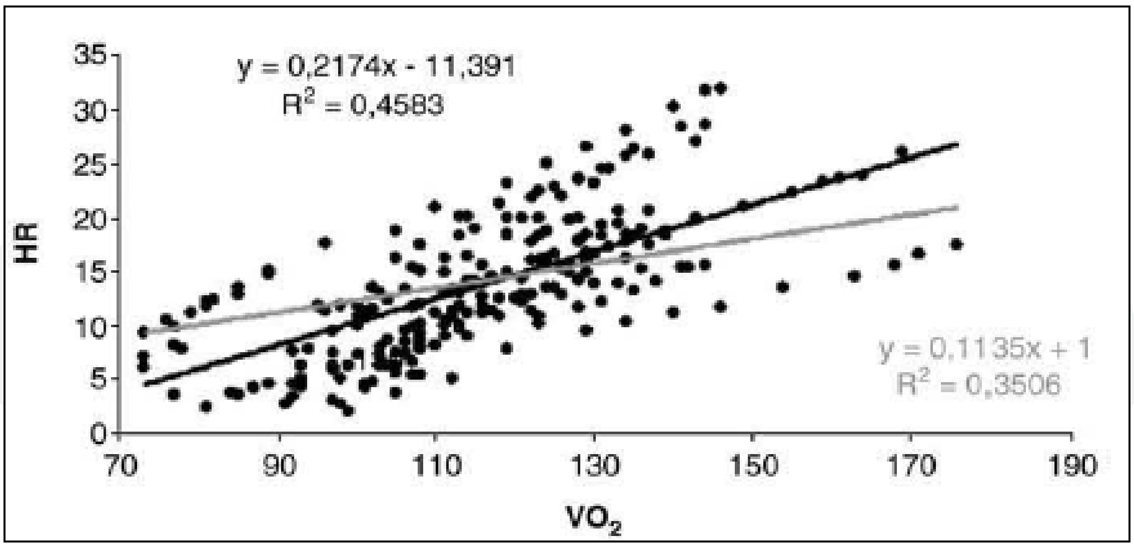


Fig. 7. Heart rate (HR) and peak oxygen consumption ($VO_2$)

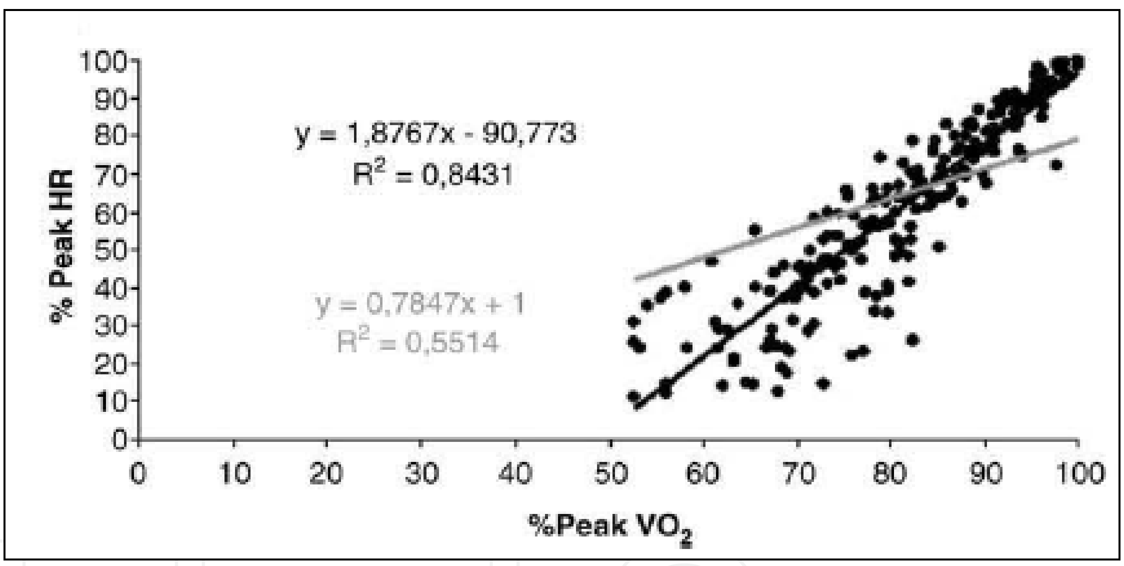


Fig. 8. The plot represents stage by stage regression of the cardiopulmonary exercise test. The grey is the identity line and the black line is regression line. Linear regression between 0 intercept and 1 intercept to percentage of heart rate reserve (%HRR) and percentage of oxygen consumption reserve (%$VO_2$R) of each patient.

The increased of muscle work and/or activation of the neurohormonal system, in order to maintain, reduced or increase blood pressure and heart rate as an answer to exercise is mainly responsible for the decrease in physical capacity among heart transplant recipients. This decrease in physical capacity after transplantation leads to insufficient production of nitric oxide (Fischer, 2005) and prostacyclin (Guimaraes, 2007), as well as hyperemia dysfunctional, and activation of other compensatory mechanisms. This occurs mainly when there is increased muscle work and/or activation of the neurohormonal system, in order to perform maintenance, reduced or increased blood pressure and heart rate in response to exercise intensity (Poston, 1999; Carvalho, 2009c).

It has also been reported that physical work capacity in heart transplant recipients decrease typically 40% of age-predicted normal levels (Goodman, 2007).

Finally, the reduction in arterial compliance observed after transplant may be due to changes on endothelial dysfunction or vascular mechanisms. Moreover, greater sympathetic nerve activity can lead to increased smooth muscle tone of arteries and, consequently, increase of the vessels stiffness (Taylor, 2003; Degertekin, 2002).

## 4. Exercise program in heart transplanted patients

Regular physical activity has played important role in the improvement of quality, as demonstrated in studies because regular physical activity may revert or diminish the physiological alterations in transplanted patients (Fig.9 ) (Guimarães, 2004).

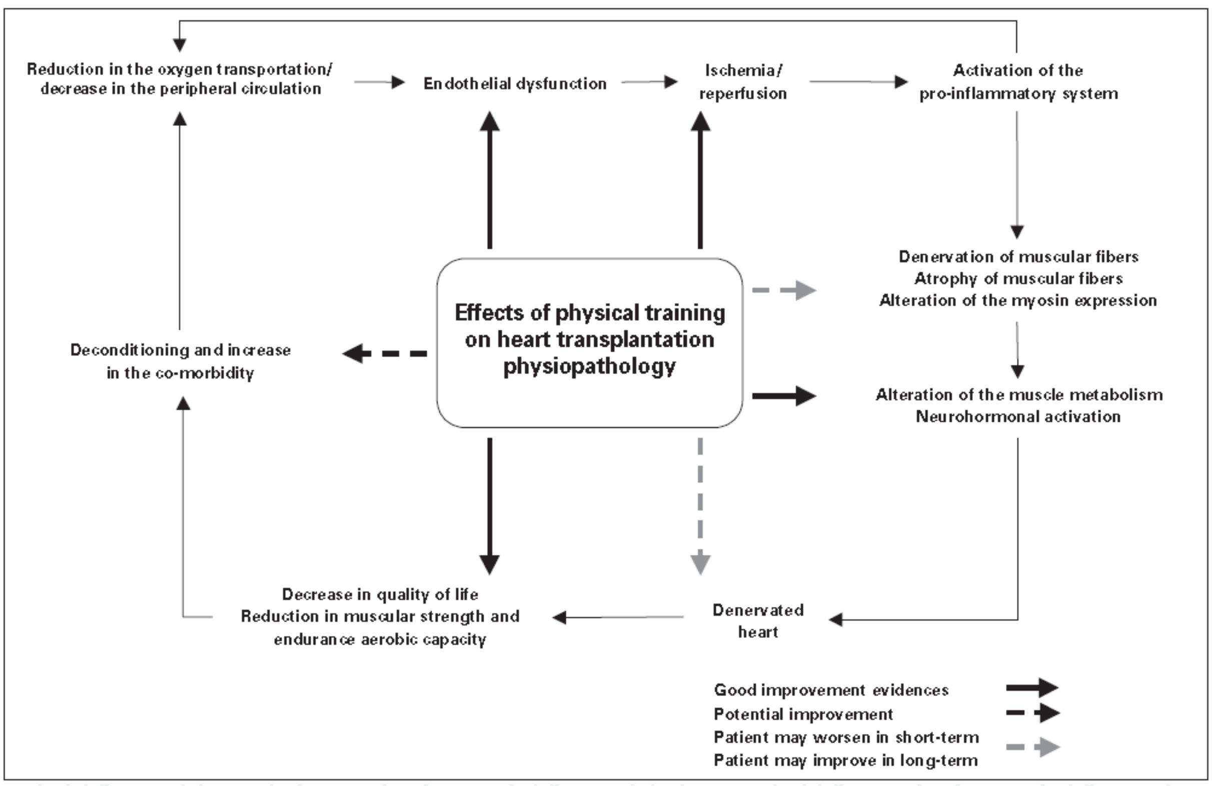


Fig. 9. Association between physical capacity and heart transplantation and the potential role of physical training on the systemic improvement, on the physiopathological effect, on quality of life and on functional capacity

## 5. Exercise in ICU (intensive care unit)

Even in the earliest days after surgery, the physical therapist will begin to work. Exercise in this scenario is important for several reasons. It aims to restore pulmonary capacity once a median sternotomy procedure is performed and can cause diaphragm reflex inhibition, pain whenever breathing. It also looks for reducing chances of getting lung infections, thromboembolism, bedsores and decrements in peak oxygen consumption ($VO_2$peak) and related cardiovascular parameters (which may regress approximately 26% within the first 1 to 3 weeks of sustained bed rest) (Braith, 2000) .

Types of exercise include respiratory ones, either with or without equipments, exercises in bed, changing positions in bed, sitting, standing and walking.

Recipients remain in hospital post-transplant depending on their general improvement and lack of complication. Different from pretransplantation hospitalization, which may be prolonged for inotropic support or a ventricular assist device, they leave hospitals soon after surgery because of the risk of infection in a hospital (usually after 2 weeks if there aren't any complications) and are discharged from the unit to a rehabilitation program.

## 6. Exercise prescription

After heart transplantation patients show physical deconditioning, muscular atrophy, weakness and lower maximal aerobic capacity so regular aerobic/strength training have been studied in both post-heart transplant recipients adults (Keteyian, 1991) and children (Patel, 2008) to study whether it would improve exercise performance. Most programs currently treating orthotopic transplant patients usually provide 6-12 week of exercise training.

In general overview, exercise program improves maximal O2 consumption and, by improving peak heart rate and also improves $O_2$ delivery in adults after a 10-week exercise program (Keteyian, 1991).

Benefits have also been found in children. After an exercise intervention consisted of aerobic exercise (either running or bicycling for 30 minutes three days/week), plus strength training was performed with elastic bands to specifically exercise biceps and triceps groups for 15-20 min/session was responsible for pediatric heart recipients improvement in their endurance time, peak oxygen consumption and strength.

Studies on aerobic training after cardiac transplantation have distinct characteristics of intensity, type, duration and frequency, so that the evaluation of the results on the effects on the cardiovascular system should be interpreted carefully. Moreover, the intensity of the exercise may enable or help to depress the immune system by hormonal, metabolic and mechanical mechanisms; however, there are no studies about the effect of intensity on the immune response in this population. (Guimarães, 1999).

Knowing the exercise stress tests is necessary information in order to develop a correct exercise prescription. Naughton protocol is more recommended for these patients. Among the parameters, heart rate reflects the cardiac stress, and the rest and maximum, or the metabolic thresholds are used to prescribe the range of exercise intensity and monitor physical training (initially 70% heart rate reserve). (Carvalho, 2009a; Braith, 2000).

Blood pressure during exercise reflects a combination of increased cardiac output and reduced peripheral resistance, thus it should also be considered when prescribing exercise and monitoring it. These hemodynamic variables must be observed during the rehabilitation program for either progression or discontinuation, if necessary.

## 7. Physical exercise after hospital discharge

Nine months after the surgery procedure, partial reinnervation shows up, but it, yet, promotes inefficient control of heart rate (Bernardini, 1998). This reinnervation can be partially restored over the years. Although heart rate increases after an exercise program (Schwaiblmair, 1999), it remains attenuated, thus, not worth to precise monitor cardiovascular and aerobic exercise prescription. Around 80% of the maximum age-adjusted value could be considered an effort near the maximum, so, it may be a parameter for prescribing exercise (Carvalho, 2009a).

Another good method to prescribe aerobic exercise training in heart transplant recipients without a cardiopulmonary exercise test with gas analysis is by the ratings of perceived exertion (Carvalho, 2009b). In order to achieve this purpose subjects are encouraged to do exercise between a relatively easy rhythm and a slightly tiring one, between 11 and 13 on the Borg Scale as seen in Table 1. (Guimarães, 2008).

| Borg Scale | Self-subject fatigue association |
|---|---|
| 6 | |
| 7 | Very easy |
| 8 | |
| 9 | Easy |
| 10 | |
| 11 | Relatively easy |
| 12 | |
| 13 | Slightly tiring |
| 14 | |
| 15 | Tiring |
| 16 | |
| 17 | Very tiring |
| 18 | |
| 19 | Exhaustive |
| 20 | |

Table 1. Borg Scale of subject fatigue.

Comparing heart transplant recipients from our lab at Heart Failure Clinics of Heart Institute before and after an exercise program, a more efficient parasympathetic response can be identified (compare the blue line on Figure 3 to the one in Figure 10). In sedentary people after transplantation exercise recovery is significantly slower than in healthy ones (Figure 1), but it becomes close to normal after exercise (Figure 2). This may be explained by the partial restoring function of the **autonomic nervous system** (ANS), especially of the parasympathetic system because a more efficient stimulation in concern of a reduction in heart rate becomes present.

Specific time exercise program is, yet, not precise in order to restore ANS due to total reinnervation, but current data indicates that combined therapy (drug stimulation of reinnervating sympathetic neurons and exercise) can establish better ANS function after orthotopic heart transplantation (Burke, 1995).

Published studies on heart transplant recipients' rehabilitation have shown better hemodynamic function (Braith, 1998b) with dif\ferent training programs. It is clear that physical activity immediately following heart transplantation and adherence to an

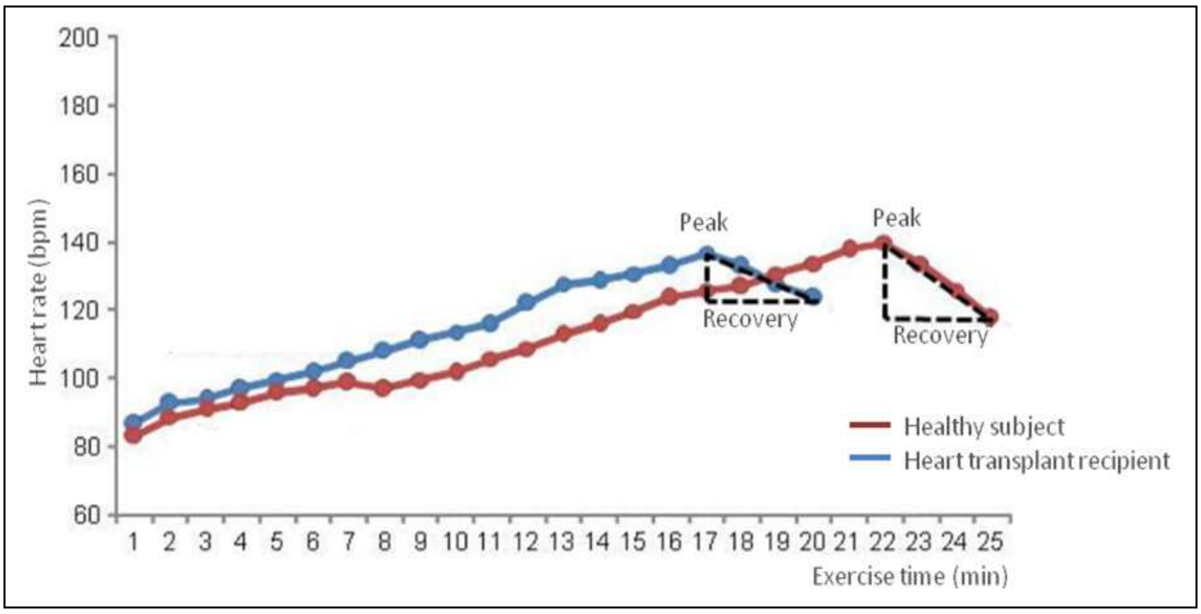


Fig. 10. HR representation after a 12-week exercise program in a healthy subject (in red) and in a heart transplantation recipient (in blue).

individualized program that promotes an active life style helps to restore cardiovascular function (Goodman, 2007). Programs include aerobic exercise, weightlifting, flexibility exercise, or training in both land and water.

Each of the programs has a particularity. Their specifications and attention are concerned to type of exercise, intensity, volume and frequency of the sections. Knowing these differences may help one to better prescribe a training exercise program (Table 2.)

## 8. Aerobic exercise

Aerobic exercise such as walking, running and cycle ergometer can be prescribed on a continuous or interval kind, depending on experience or protocol used by rehabilitation service. Nonetheless, the intensity of aerobic exercise should be determined according to the workload, if possible at the respiratory compensation point reached during the cardiopulmonary exercise test in combination to exercise at a pace between "relatively easy and slightly tiring", between 11 and 13 on the Borg Scale (Guimarães, 2008). Exercise sessions should be held three times a week with a 5-minute warm up, 30 minutes of aerobic training followed by 5 minutes of recovery and 20 minutes of strength exercises.

## 9. Weightlifting

Exercise with weights, adjacent to the aerobic exercises, have been recommended after heart transplantation, although hemodynamic function is restored to near normal values, this group of patients still shows a significant decrease in muscle mass and strength, bone rarefaction and histochemical changes in muscle fiber type from type I to type II (Braith, 1998; Lindenfeld, 2004a, Lindenfeld, 2004b).

These persistent changes in the transplant can be minimized with regular practice of resistance training with weights and moderate intensity that must be performed in small

| Specification | Aerobic | Weightlifting | | Flexibility | Water |
|---|---|---|---|---|---|
| | | Static | Dynamic | | |
| Type | Interval and continuous training | Main muscle groups | 8 to 10 (main muscle groups) | Main muscle groups | Walking (in hot water at 30 or 31$^0$C) |
| Intensity[Ŧ] | 60% to 70% peak $VO_2$ HR between AT and RCP | 30 to 75%MVC | 40% to 80% 1MR | light to moderate | 60% to 70% peak $VO_2$ HR between AT and RCP |
| Volume[ŧ] | 30 to 40 min | 1 to 10 x 6 s | 1 x 4 to 6 (avoiding fatigue) | 3 a 5 repetitions | 30 a 40 min |
| Frequency | 5 x a week | 2 x a week$^{-1}$ (5 – 10 x a day)[§] | 2 x a week (maximal) | 5 x a week | 2 x a week |
| Progression | Respect the Borg scale perception between 13 and 15 | Tolerable ROM (initial); Perform contraction under different ROM whenever pain and inflammation get lower. Add load when strength is increased | 5-10%-load (a week) · | In order to stretch soft tissue and either to keep or increase ROM | Respect the Borg scale between 13 and 15 |
| Attention | BP lowering during exercise sections whenever Borg scale perception is greater than previous sections. | Contraction > 10 s may increase BP | - | Respect morphological limits in order not to cause injuries. | BP lowering during exercise sections whenever Borg scale perception is greater than previous sections. |

Table 2. Practical recommendations for exercise prescription. MVC: maximal voluntary contraction; AT: anaerobic threshold; RCP: respiratory compensation point; 1MR: one maximal repetition test; ROM: range of motion; BP: blood pressure; [Ŧ] Subjects were encouraged to begin under their low threshold and increase intensity up to their highest threshold, progressively, as tolerated. [ŧ] Static: 1) from a 6-second contraction at first, to an 8 or 10-second contraction, 2) wait 20-second intermission between contractions; Dynamic: one series of 4 or 6 repetitions without any muscle fatigue; [§]subjects should go from exercising twice a day to 5-10 times a day.

series, with a maximum of ten repetitions for flexors and extensors groups of the upper and lower limbs. This results in reduction of osteoporosis and skeletal muscle myopathies (caused by the use of glucocorticoids), and contributes to the gain in muscle strength and increase in $VO_2$ peak, at the same time (Lindenfeld, 2004b).

## 10. Flexibility exercises

Stretching exercises should be conducted to promote gains on range of motion, balance, to stretch the muscles of the neck, lower back, upper and lower limbs. Exercise with elastic can be performed in small series of ten repetitions for each muscle prioritizing posterior trunk and involving large joints of hip, knee, elbow and shoulder.

## 11. Aquatic exercise

Physical activity in aquatic environment is little reported after cardiac transplantation. However, a case report demonstrated potential benefits of training in heated swimming pool at 30-31°C, 1.40 meters of depth, with sessions of 40 minutes of exercise: 5-minute warm up, 15 minutes of walking on water, 15-minute workout with weights involving large joints and 5 minutes of relaxation. Physical activity in aquatic environment is a well established method of rehabilitation for patients with significant functional limitations and has proven to be effective in cases of obesity after transplantation.

## 12. Implication of drug therapy in exercise

During the last 25 years there has been a significant increase in survival of patients undergoing heart transplantation (Guba, 2002), generally, as a result of advanced immunosuppressive therapy to control organ rejection since the transplanted heart originates from another organism, and the recipient's immune system attempt to reject it.

But the most widely used therapy is the combination of several drugs that have different modes of action and potential. Some side effects of the use of immunosuppressive medication may appear early in the drug treatment and can be minimized with appropriate modifications and adjustments of schedules and doses (Chart 1, 2 and 3).

Since the late onset side effects must be controlled with the inclusion of specific drugs to control the clinical signs and symptoms of the patient. The latter is represented by corticosteroids, calcineurin inhibitors and TOR inhibitors.

Corticosteroids (Prednisone) act as a nonspecific anti-inflammatory, so the rejection process suffers a direct influence of the recruitment and activation of T-helper lymphocytes. The TOR inhibitors: Tacrolimus (also known as FK-506 or Fujimycin) has a similar action to cyclosporine and is used as a second option to cyclosporine, and Sirolimus, also known as rapamycin, has an inhibitory effect on activation and proliferation of T cells. So, these immunosupressive drugs reduce the infection risk, but may have some undesirable adverse effects (Bortolotto, 1997; Fiorelli, 1996), such as nephrotoxic effects, artery damage and narrowing, left ventricle hypertrophy, increased likelihood of bone fractures and infections. These entire side effects contribute to related health problems over time, so it makes professional responsible for their physical rehabilitation more attempted to effects during exercise as increased blood pressure, transient ischemic attack (TIA).

Moreover, there has been growing clinical consensus that specific training regimens (endurance and resistance) in heart transplant recipients can be efficacious adjunctive therapies in the prevention of immunosuppression-induced side effects and may be an effective countermeasure for corticosteroid-induced osteoporosis and skeletal muscle myopathy.

Heart transplanted recipients who participate in specific resistance training programs successfully restore bone mineral density (BMD) in both the axial and appendicular skeleton to pretransplantation levels, increase lean mass to levels greater than pretransplantation, and reduce body fat. In contrast, those who do not participate in resistance training lose approximately 15% BMD from the lumbar spine early in the postoperative period and experience further gradual reductions in BMD and muscle mass late after transplantation. (Braith, 2000)

| Medicine | Side Effects | Exercise limitations |
|---|---|---|
| Corticosteroids (Prednisone) | Hypertention | Left ventricle hypertrophy, damage to the arteries, brain, heart, kidney and even sudden death. |
| | Hyperglycemia | Damage to the arteries, brain, heart, and kidney. |
| | Hyperlipidemia | Damage to the arteries, brain, heart, and kidney. |
| | Diabetes | Damage to the arteries, brain, heart, and kidney, peripheral neuropathy, loss of balance and falls. |
| | Weight gain | Gallstones and Diabetes. |
| | Osteoporosis | Bone fracture |
| | Cushingoid appearance | NA |
| | Mood changes | Not adherence to an exercise protocol |
| | Cataract | Incoordination and loss of balance |
| Calcineurin inhibitors (Cyclosporine) | Kidney vasoconstriction | Nephrotoxicity and sodium retention (which contribute to body plasma volume) |
| | Hyperkalemia | Cardiopulmonary arrest |
| | Hypertension | Left ventricle hypertrophy, damage to the arteries, brain, heart, kidney and even death. |
| | Venous thrombosis | Pulmonary thromboembolism |
| | Migraine | Not adherence to an exercise protocol |
| | Tremor | Incoordination |
| | Paresthesia | Loss of balance and falls |
| | Gout | Pain and ROM limitation |
| | Gum hyperplasia | NA |
| | Hepatotoxicity | NA |

Chart 1. Side effects and mainly corticosteroids and calcineurin inhibitor interferences. NA: not applicable. ROM: range of motion.

| Medicine | Side Effects | Exercise limitations |
|---|---|---|
| Tacrolimus | Kidney vasoconstriction | Nephrotoxicity (similar to cyclosporine) |
| | Hypertension* | Left ventricle hypertrophy, damage to the arteries, brain, heart, kidney and even sudden death. |
| | Hyperlipidemia* | Damage to the arteries, brain, heart, and kidney. |
| | Diabetes # | Damage to the arteries, brain, heart, and kidney, peripheral neuropathy, loss of balance and falls. |
| Sirolimus | Bone marrow aplasia | Thrombocytopenia, anemia and leukopenia |
| | Hyperlipidemia | Damage to the arteries, brain, heart, and kidney. |
| | Peripheral edema | Difficulty on progressing ROM, loss of balance and falls. |
| | Wound healing impairment. | Incapacity of moving the affected area, not adherence to an exercise protocol. |

Chart 2. Side effects and mainly TOR inhibitors interferences. * fewer than cyclosporine's side-effect; # greater than cyclosporine's side-effect;

| Medicine | Side Effects | Exercise limitations |
|---|---|---|
| Azathioprine | Neutropenia and thrombocytopenia | Increased risk of infections, venous thrombosis, pulmonary thromboembolism anemia, and bleeding. |
| | Nausea, vomit | Not adherence to an exercise protocol |
| | Pancreatitis, hepatotoxicity and cancer. | NA |
| Mycophenolate | Neutropenia | Increased risk of infections |
| | Nausea, vomit | Not adherence to an exercise protocol |

Chart 3. Side effects and mainly antiproliferative agents interferences.

## 13. Final comments

Heart transplantation is indicated as therapy for patients in the end stage of heart failure. These patients, despite the fact they trade their damaged hearts for functional ones, they remain with several impairments, as muscle weakness, and develop some other disabilities because of the transplantation procedure itself and due to the use of required drugs to control rejection.

Regular physical activity in general has shown potential benefits for the control and reduction of chronic degenerative diseases, which should be incorporated as a therapeutic agent after cardiac transplantation. However, studies on cardiac rehabilitation in transplanted patients are isolated and inconclusive regarding the answer in the long term effect on the immune system, neurohormonal, musculoskeletal and adherence to the program. Furthermore, these studies refer only to cardiovascular training, leaving aside structural and postural changes, such as rotations, shoulder girdle and pelvic misalignments-scapular of the patient, which can be found in the majority who have some functional deviation as stiffed vertebral joints and shorten muscle. Another important aspect that we consider is the socio-cultural reference of transplant patients, which can often limit or even refuse to participate on a physical training program.

The effect of physical conditioning after transplantation is mainly attributed to higher peripheral efficiency, but there has also been found a degree of cardiac adaptation.

In current practice of heart transplant recipients' therapy, further studies are needed to elucidate the role of physical activity on the interaction of physiological and clinical responses in this group of patients.

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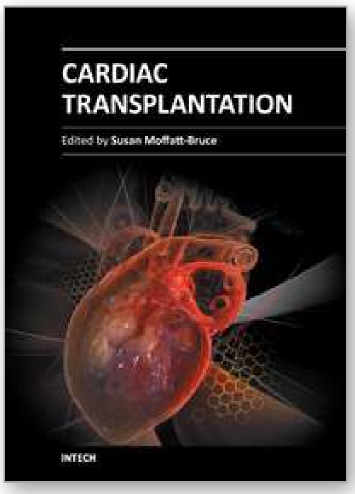


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We are truly in an era of change not only in terms of technology but in the type of patient we are caring for. That is why I feel this book is exciting in that it presents the team approach to the transplant patient. I am confident that the pioneers of cardiac transplantation would be pleased with our response to challenges in healthcare today and be pleased with the final product.