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The Effect of High Intensity Interval Training on Cardiac Allograft Vasculopathy

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The Effect of High Intensity Interval Training on Cardiac Allograft Vasculopathy

Abstract

Background:

Cardiac allograft vasculopathy (CAV) is a multifactorial disease process that occurs in heart transplant (HTx) patients and has both immunologic and nonimmunologic components. Exercise has been proven to reduce the progression of CAV. The extent to which high intensity interval training (HIIT) can be utilized and its efficacy for delaying CAV is still being researched.

Methods:

A thorough search was conducted on three different databases including: MEDLINE-Ovid, Web of Science, and CINAHL. The keywords used during the search were "heart transplantation" and "high intensity interval training." The search was narrowed to include only articles written in the past 5 years and articles published in the English language. The quality of evidence was assessed using GRADE.

Results:

Two articles were found that met inclusion criteria. The studies differed from each other in what was considered the control group. The Dal et al study compared HIIT training to moderate exercise in a cross over trial with a 5-month washout period. Throughout the study endothelial wall damage was recorded. In the Nytrøen et al study participants were placed into a control or HIIT group. The HIIT group received HIIT therapy while the control was instructed to not modify their workouts for the duration of the study. At the end of the study endothelial wall measurements were measured via arterial ultrasound.

Conclusion:

These studies showed that HIIT therapy can delay the onset of CAV; however, due to the inadequacy of one of the studies it could not be determined if HIIT was better than continuous moderate exercise (CME). The Dall et al group did not have the sensitivity needed in their measurements of the endothelial wall damage to determine if it was more effective than CME. To determine the possible benefits of HIIT more research needs to be conducted. Since CAV is such a risk to HTx patients the optimal exercise program to delay CAV is of critical importance.

Degree Type

Capstone Project

Degree Name

Master of Science in Physician Assistant Studies

Keywords

High intensity interval training, heart transplant, Cardiac Allograft Vasculopathy

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The Effect of High Intensity Interval Training on Cardiac Allograft Vasculopathy

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A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

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Biography

Daniel Ells is a Connecticut native and graduated from Quinnipiac University in 2012 majoring in Health Science Studies with minors in Chemistry and Psychology. While at Quinnipiac Daniel worked as an EMT and a physical therapist aide. After completing his undergraduate degree he was involved in substance abuse research at the Yale school of Medicine for 5 years prior to attending Pacific University.

Kevin Palm is originally from Hollister California and completed his undergraduate studies at California State University of Sacramento. His Bachelors of Science degree had a focus in Biomedical Science. After completing his degree in 2014 he scribed in three emergency departments throughout California prior to coming to Pacific University.

Abstract

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Two articles were found that met inclusion criteria. The studies differed from each other in what was considered the control group. The Dal et al study compared HIIT training to moderate exercise in a cross over trial with a 5-month washout period. Throughout the study endothelial wall damage was recorded. In the Nytrøen et al study participants were placed into a control or HIIT group. The HIIT group received HIIT therapy while the control was instructed to not modify their workouts for the duration of the study. At the end of the study endothelial wall measurements were measured via arterial ultrasound.

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Keywords: High intensity interval training, heart transplant, cardiac allograft vasculopathy

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To *our classmates, loved ones, and friends*: Thank you for your support through these crazy years. We needed the support and the encouragement you shared with us, thank you for being there when we needed you.

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Table 1. Quality Assessment of Reviewed Articles

List of Abbreviations

| | |
|------|----------------------------------|
| CAV | Coronary Artery Vasculopathy |
| CME | Continued Moderate Exercise |
| FMD | Flow-mediated dilation |
| HIIT | High-Intensity Interval Training |
| HTx | Heart Transplant |
| PAT | Pulse Amplitude Tomography |
| RHI | Reactive Hyperemia Index |

The Effect of High Intensity Interval Training on Cardiac Allograft Vasculopathy

BACKGROUND

Heart transplant (HTx) recipients face a host of challenges after their operation ranging from, but not limited to, rejection, infection, malignancy, and vascular disease. One of the most prominent and fatal of these challenges is a coronary vascular complication known as coronary artery vasculopathy (CAV). CAV is seen in more than 50 percent of heart transplant patients in the first several years following the procedure¹ and is one of the leading causes of morbidity and late mortality in heart transplantation patients.²

The pathogenesis of CAV is a complex and a multifactorial process that has both immunologic and nonimmunologic components to it. The process begins with endothelial injury that leads to intimal thickening and eventual diffuse circumferential smooth muscle hyperplasia.³ This initial injury can be caused by many things. We know the foreign vessels can initiate activation of both the humoral and cellular immune system, which results in progressive damage to the foreign coronary vessels.⁴ It seems that other important nonimmunologic factors have also been identified in playing a role in the development of the disease. Factors that have been linked to the development of CAV include: hyperlipidemia, hypertension, obesity, older age, cytomegalovirus infection, immunosuppressive drugs, and insulin resistance or poor glycemic control.^{3,5} To reduce morbidity and mortality in HTx patients the development and prevention of CAV must be explored.

There are a few ways to observe the development of CAV. One such way would be to utilize intravascular ultrasonography to measure the change in intimal thickness within the coronary arteries.¹ Another way would be to look at endothelial health, which can be an early indicator of the development of vessel damage.^{6,7} Endothelial health has been traditionally

measured using brachial flow-mediated dilation (FMD) measurements. A newer clinical tool to measure endothelial function is the digital pulse amplitude tonometry (PAT). The studies we reviewed in this review looked at either intimal thickness or endothelial health to gauge the extent of disease in follow up.

The current standard to reduce the risk of developing CAV is to begin antiproliferative drugs and statins shortly after transplantation.⁸ In addition to drug therapy, it has been proposed that exercise, in those that are healthy enough to participate, could also be beneficial in reducing the risk of developing CAV. Exercise has been shown to be very beneficial in the treatment of patients with coronary vascular disease and in treating the risk factors associated with development of CAV including: hyperlipidemia, hypertension, obesity, and poor glycemic control.⁹⁻¹¹ Recently, exercise and its effectiveness in reducing the risk of developing CAV has been a topic targeted by researchers.^{12,13} Currently the standard for prophylactic treatment of CAV includes an exercise regimen along with antiproliferative pharmacologic agents, and a modification of common risk factors like hypertension, hyperlipidemia, hyperglycemia, obesity, and smoking.³ But what type of exercise is most beneficial for this specific patient population is still largely unknown.

Recent research shows that higher intensity exercise is superior to moderate continuous exercise in patients with coronary vascular disease and stable heart failure.^{14,15} Although some research has been done, the best type of exercise to prevent CAV in HTx patients has not been thoroughly examined. With recent research showing that high intensity interval training (HIIT) is well tolerated in HTx patients,^{12,13,16-19} this review looks at the research that has been done in regards of exercise intensity and the prevention of CAV in HTx patients.

METHODS

A thorough search was conducted on three different databases including: MEDLINE-Ovid, Web of Science, and CINAHL. The keywords used during the search were “heart transplantation” and “high intensity interval training.” The search was narrowed to include only articles written in the past 5 years and articles published in the English. Search results were then narrowed even further to include only articles that focused on vascular health as their major outcome. Works cited pages of included articles were then reviewed to include other possible relevant studies. After applying inclusion criteria to the database results, articles were then assessed for quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).²⁰

RESULTS

The initial literature search yielded a total of 23 articles for review. After removal of duplicate papers and application of inclusion criteria, two articles were included. There were multiple researched papers produced from two data sets by two different research groups. One research group compared HIIT to continuous moderate exercise (CME)¹ while the other group compared HIIT to a control with no structured exercise regime just medication therapy.² Only one article from each research group met inclusion criteria due to the other papers not focusing on vascular health as their main outcome measured. See Table 1.

Nytrøen et al

This study¹³ was published in 2013 and is a randomized clinical trial consisting of 43 post heart transplant patients. The study looked at the effectiveness of HIIT training vs a control group which received full medical care but no additional structured exercise regimen. There were two papers^{13, 16} produced from this same randomized clinical trial. The one included in this

analysis focused on the progression of CAV by monitoring patients' coronary vessels via intravascular ultrasound. By using intravascular ultrasound, the team was able to evaluate percent atheroma volume, total atheroma volume, total plaque volume, and maximal intimal thickness to assess the health of the coronary vessels and progression of CAV over the year of the study.¹³

For this study 192 potential participants were screened for eligibility. Of the 192 potential participants 57 met the study's inclusion criteria. The participant had to be over 18 years of age, 1-8 years post-transplant, be in optimal medical treatment, be in a stable condition, be able to perform maximal exercise on a treadmill, and have a willingness to participate in a 1-year HIIT exercise program. Of the 57 that were initially recruited, 5 did not complete the trial. One withdrew from the study and the other 4 were, "excluded because of logistics."¹³

The 52 participants were then randomly assigned to 2 groups by a computer randomization sequence. The intervention group underwent 3 separate 8-week periods where they participated in supervised high intensity interval training 3 times a week. The HIIT program consisted of bouts of 4 minutes of exercise performed at or above 91.5 % of the patient's maximal heart rate. In between the 8-week periods the HIIT group was encouraged to continue with exercise but there was no formal supervised training provided. Along with a formal exercise program the intervention group also received full medical therapy including immunosuppressive therapy and statins. The control group had no formal exercise training but received full medical therapy and exercise was encouraged in the group. In the 3 months leading up to follow up testing the control group reported that 33% had exercised once a week or less, 43% exercised 2-3 times per week, and 24% had exercised 4 or more times a week.¹³

Both the HIIT group and control group had baseline testing done initially and again after 1 year of treatment. Testing included intravascular ultrasound, peak flow VO₂, and blood draws including a lipid panel, blood glucose testing, creatinine, CRP, and interleukin levels. The article that was included in this review focused on intravascular ultrasound results as a means to determine the progression of CAV in the 2 groups during the year of the study. The researchers had a blind technician perform the ultrasound and report the results. From the ultrasound results the researchers calculated change in percent atheroma volume, total atheroma volume, total plaque volume, and maximal intimal thickness.¹³ The other testing results mentioned above were discussed further in an earlier paper by the research group.¹⁶

The HIIT group showed a statistically significant smaller increase in percent atheroma volume, total atheroma volume, and total plaque volume when compared to the control group. Percent atheroma volume increased by 0.9% {-0.3% to 1.9% } in the HIIT group while it increased by 2.5% {1.6% to 3.5% } in the control group (p = 0.021). Total atheroma increased by 0.3% mm³/mm {0.0 to 0.6} in the HIIT group and increased by 1.1% mm³/mm {0.6% to 1.7% } in the control group (p = 0.054). Total plaque volume increased by 8.0 mm³ {0.3 to 15.7} in the HIIT group and increased by 25.6 mm³ {14.8 to 36.4} in the control group (p = 0.011). It was also observed that maximal intimal thickness increased at a faster rate in the control group but the findings were not statistically significant. A qualitative analysis of the plaque was also done in the 2 groups but there was no significant difference between the groups.¹³

Dall et al

This study¹² was published in 2015 and is a randomized control crossover trial in HTx patients aimed at examining the difference between continued moderate exercise (CME) and HIIT. The outcomes of this study were published into multiple papers, the paper used in this

analysis focused on vascular function, biomarkers, and quality of life as primary outcomes. Vascular health was assessed by the utilization of EndoPAT 2000. This device measures endothelial stiffness and function.¹²

Participants for the study were screened for eligibility and of the 20 patients screened, 17 were deemed eligible. Exclusion criteria included HTx within a year, patients younger than 18 years, and patients deemed unstable due to severe CAV, malignant disease, or multi-organ transplant. The participants also needed to be physically capable to perform the workouts. Of the 17 participants that started the study 16 completed it.¹²

An independent researcher not involved with the investigation assisted in the envelope randomization of participants to the HIIT washout CME group or CME washout HIIT group. The workout regimens took place on ergometer bikes 3 times per week under supervision. Each HIIT session was 30 minutes long and consisted of 16 minutes of interval training, at 4-, 2-, and 1-minute intervals of high intensity exercise (VO_2 peak > 80%) each of the intervals was separated by 2 minutes of moderate exercise at 60% VO_2 peak. The CME sessions consisted of 45 minutes of biking at 60% to 70% VO_2 peak. All sessions, for both groups, began and ended with 10-minute warm up and cool down sessions. Each program, CME and HIIT, took place for 12 weeks. Following the 12-week workout program participants went into a 5-month washout period where they were told to exercise as usual. Then participants returned to complete the other arm of the experiment for 12 more weeks of exercise.¹²

The EndoPAT 2000, used to examine endothelial function, was used throughout the study to assess the vascular benefits of HIIT and CME. Data points were collected at baseline and follow up of each exercise program. The measurement of endothelial function is described as the reactive hyperemia index (RHI). The noninvasive, operator independent EndoPAT 2000

evaluates the endothelial function by measuring a pulsatile volume change in the fingertip before and after the brachial artery is occluded. A baseline measurement is obtained and then a blood pressure cuff is used to occlude the artery for 5 minutes at a pressure >200 mm Hg. After the cuff is released the EndoPAT 2000 reads the hyperemic response and the RHI is automatically calculated. The augmentation index (AI) is created in an analysis of the pulse wave data. The AI is correlated to an increase arterial stiffness. As AI increases so does arterial stiffness.¹²

In the HIIT and CME branches of the study the RHI at baseline was 2.2. The follow up RHI for was 2.5 and 2.2, respectively. There was no significant statistical difference between groups. Similarly there was no significant difference noted in arterial wall stiffness between the 2 groups. The effect of the workout intervention was lost after the 5-month period of no exercise and then participants began the other workout regimen. The study went on to discuss other outcomes such as biomarkers and quality of life which were not outcomes in Nytrøen et al and are not compared in this analysis.¹²

DISCUSSION

CAV is a progressive and detrimental disease that occurs in post heart transplant patients. It remains one of the major causes of death in the late post-transplant phase.² To treat CAV a multidisciplinary approach needs to be implemented to adjust many aspects of a patient's life. Although medication therapy with statins and anti-proliferative drugs have been shown to be effective in slowing progression of CAV, therapies used today are still imperfect and exercise is being evaluated as a therapy to further decrease the risk of developing CAV.^{12,16} According to the findings of the included studies,^{12,13} HIIT therapy can be an effective tool to slow the progression of CAV when used in conjunction with medical therapy. Although, more testing

needs to be done to determine how soon after transplant this therapy can be initiated or if it can be tolerated in individuals that are less than stable post-transplant.

The study done by Nytrøen et al¹² found that HIIT was significantly better at slowing the progression of CAV when compared to a control group only receiving medical therapy. This result proves that HIIT can be an effective therapy used to treat CAV. It is not surprising that exercise yielded slower CAV progression; as it is known, exercise is cardiovascularly protective and can decrease risk factors associated with the development of CAV.²¹

Nytrøen et al¹³ may have had some biases within the study protocol. Over 190 participants were screened for this study and only 26 of those ended up participating in the HIIT program. The inclusion criteria were very strict and removed over two thirds of the participants that were screened initially. The study required that the patient be stable post-transplant and willing to participate in a yearlong HIIT program which removed a majority of the potential participants. This presents a possible selection bias. If the study only looked at stable patients then maybe these patients had a decreased risk of developing CAV just based on the fact that they were in better condition following their transplant procedure. This potential bias makes it difficult to assess whether or not HIIT could be an appropriate therapy for all post-op HTx patients. Similarly, Dall et al¹ had a small cohort size of 16 and could have had similar risk of biases present.

The study produced by Dall et al¹² showed that there was no difference in endothelial function between HIIT and CME. However, the author and colleagues stated that the test they used to measure endothelial function, the EndoPAT 2000, is not as sensitive as a test that was used in a prior study.¹² The study that used the more sensitive FMD test found that patients that had done HIIT had significantly better FMD results when compared to a group that did only

CME.¹² This study was not included in this analysis as it was published over 5 years ago. Additionally, Dall et al¹ looked at many primary outcomes and so did not use the best test to evaluate endothelial function. This study¹² discusses the limitations of the EndoPAT 2000 test in their report stating that FMD testing is a better test for evaluating the health of endothelium. This may be a source of inconsistency or indirectness in the data.

Using the information gathered from these two studies^{12,13} clinicians can consider HIIT a viable therapy for post-op heart transplant patients with a few considerations. First the patient needs to be stable enough to tolerate the therapy. Another consideration is that medication and lifestyle changes should also still be implemented and it is unlikely that HIIT or any other exercise training is going to prevent the development of CAV as a monotherapy. Moving forward clinicians should investigate to see if new evidence continues to suggest HIIT as a viable exercise regimen for stable post heart-transplant patients.

CONCLUSION

High intensity interval training is a viable therapy to slow the progression of CAV when added to a stable post heart-transplant patient's treatment plan. HIIT has been shown to be better at slowing the progression of CAV when compared to patients receiving no structured exercise therapy and it has been shown to be equivalent to continued moderate exercise. Since CAV is a widespread disease seen in post heart transplant patients and has high mortality and morbidity it is important to consider all potential options while treating these patients. While medication therapy with anti-proliferative drugs and statins early post-transplant is still the mainstay of treatment, the addition of an exercise regimen has been shown to be a viable addition to medication therapy. Further testing still needs to be done to evaluate if HIIT is an equivalent, better, or worse treatment method than CME in slowing the progression of CAV.

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Table 1:

| Table 1: Quality Assessment of Reviewed Articles | | | | | | | |
|---|--------|--------------------|----------------------|---------------|----------------------|------------------|---------|
| Study | Design | Downgrade Criteria | | | | | Quality |
| | | Limitations | Indirectness | Inconsistency | Imprecision | Publication bias | |
| Nytrøen et al ² | RCT | Not Serious | Not Serious | Not Serious | Not Serious | Unlikely | High |
| Dall et al ¹ | RCT | Not Serious | Serious ^a | Not Serious | Serious ^b | Unlikely | Low |

a. The device used to measure endothelial function was inadequate at measuring the outcome.
b. Small sample size