

JEPonline
Journal of
Exercise Physiologyonline

**Official Journal of The American
Society of Exercise Physiologists (ASEP)**

ISSN 1097-9751

An International Electronic Journal
Volume 3 Number 2 April 2000

Clinical Exercise Physiology

Comparison Of Exercise Responses Of Patients With Cardiac Transplantation Using 3 And 6 Minute Stage Duration Protocols

JONATHAN EHRMAN, STEVEN KETAYIAN, FRANK FEDEL and T. BARRY LEVINE

Henry Ford Heart and Vascular Institute, and the Division of Cardiovascular Medicine, Department of Internal, Medicine, Henry Ford Hospital, Detroit, MI

ABSTRACT

JONATHAN EHRMAN, STEVEN KETAYIAN, FRANK FEDEL and T. BARRY LEVINE. **Comparison Of Exercise Responses Of Patients With Cardiac Transplantation Using 3 And 6 Minute Stage Duration Protocols.** *JEPonline*, 3(2):1-5, 2000. The purpose of this investigation was to test whether there was a difference in plasma norepinephrine concentrations, heart rates, peak work rate and peak oxygen consumption values in patients who have undergone cardiac transplantation when using a 3 versus a 6 minute stage protocol. Nine males (age = 51 ± 8 years, mean \pm SD) were randomly tested by cycle ergometry on two, nonconsecutive days at 45 ± 18 months (range 16 - 59) following surgery. As expected, group mean exercise time was greater for T6 than T3 (18.7 ± 2.1 min versus 11.5 ± 1.1 min; $p < 0.05$). The group mean peak work rate tended to be greater for T3 than for T6 (117 ± 5 versus 100 ± 10 Watts, $p = 0.06$). Peak respiratory exchange ratio was greater for T3 (1.15 ± 0.0 versus 1.05 ± 0.07 , $p = 0.012$). Peak rate pressure product and rate of perceived exertion were not different. There was no significant difference between T3 and T6 for submaximal plasma norepinephrine concentration, submaximal and peak HR, or peak oxygen consumption. Peak exercise plasma norepinephrine concentration was greater for T3 than T6 (3750 ± 467 versus 3218 ± 360 pg/ml, $p = 0.013$). In conclusion, for patients with cardiac transplant, an exercise test using 6 min versus 3 min stages did not result in a different peak HR despite a lower peak plasma norepinephrine levels and greater total exercise time.

Key Words: catecholamines, heart rate

INTRODUCTION

The decentralized heart primarily increases its rate of contraction during upright exercise due to the time

course rise in plasma norepinephrine concentration (10, 11). Despite the ability to increase heart rate (HR) in response to a work rate increment, the rate of increase in HR and the peak HR in the patient with cardiac

transplant (CT) is reduced than in the person with a normally innervated heart. This response is likely the result of the absence of cardiac sympathetic efferent innervation (10, 11).

The attenuation in the response of HR in the patient with CT during exercise (10) contributes to the inability to use a HR based method to prescribe exercise intensity in these patients (8). As a result, various other methodologies such as rating of perceived exertion (7, 8, 13), percent of maximum oxygen consumption (VO_2) (7), ventilatory threshold (5, 7) and lactate threshold (4) have been recommended as a guide to prescribing exercise intensity in the patient who has undergone CT.

Olivari et al. (9) reported findings on the use of a longer duration stage protocol during exercise testing. The results demonstrated that peak HR was significantly higher in patient's with a transplanted heart who were exercise tested using a protocol in which the work rate was not increased until steady state VO_2 and HR values were achieved, as compared to a conventional Naughton treadmill protocol with 2 min stages. This was despite a greater work rate achieved during the steady state protocol. However, plasma norepinephrine concentrations were not assessed.

The purpose of this investigation was to test whether, using a 6 min versus a 3 min per stage work rate increment protocol, the plasma norepinephrine concentration and HR values differ in the above type patient. We hypothesized that an exercise test using 6 min (T6) versus 3 min (T3) stage increments in patients with cardiac transplant would result in higher plasma norepinephrine concentrations and heart rates at selected stages, and at peak exercise.

METHODS

Subjects

Nine male patients who had undergone CT and a mean age, body weight and months after surgery of: 51 ± 8 years (mean \pm SD), 89.2 ± 11.3 kg, and 45 ± 18 months (range 16-59 months), respectively, participated in the study. All patients gave informed consent and the study was approved by the hospital's Human Subjects Committee. Six subjects were transplanted secondary to dilated cardiomyopathy and three due to ischemic

cardiomyopathy. None of the patients were receiving positive inotropic or chronotropic medications. All were prescribed standard triple drug immunosuppressive therapy (prednisone, cyclosporine and Imuran), and were receiving various anti-hypertensive agents. As part of each patient's annual evaluation following transplantation, left ventricular function was assessed during cardiac catheterization within the previous 12-month period. Each patient's ejection fraction was greater than 45%.

Equipment and Experimental Protocol

In this cross over design study, each patient completed two continuous graded exercise tests. These were performed on two nonconsecutive days using a Monark cycle ergometer that was calibrated prior to each test. The order of the tests was randomly set and work rate was increased every 3 min or 6 min. Testing began at 30 Watts and increased 30 Watts/stage until volitional fatigue was achieved. An electrocardiogram rhythm strip was recorded at the end of each stage to determine heart rate. Expired air was analyzed for VO_2 using a metabolic cart (Horizon II, Sensormedics Corp., Yorba Linda, CA) which was calibrated prior to each test. VO_2 values were reported as 15 s averages.

Prior to testing each patient had an 18 gauge catheter placed in an antecubital or a dorsal hand vein. Following 30 min of quiet, supine rest a baseline blood sample (10 ml) was obtained for norepinephrine determination. Samples were also obtained at the end of each stage and at peak exercise. High-pressure liquid chromatography was used to determine plasma norepinephrine levels (1). This data was used to determine an index of beta-receptor sensitivity ($\Delta \text{HR} / \Delta$ norepinephrine concentration).

Statistical Analysis

All data are reported as the mean \pm SD. Univariate 2-way repeated measures ANOVA was used to detect a significant effect ($p \leq 0.05$). For variables where a significant interaction effect was detected (test \times stage), a post-hoc analysis was conducted using a paired t-test. For each analysis the Bonferroni multiple comparison test adjustment was used to reduce the alpha level from 0.05 to 0.013. A 2-way ANOVA with repeated measures was employed to assess the beta-receptor sensitivity index. The overall statistical power of this investigation was

80% (beta = 0.20) to detect a difference in mean values of ≥ 0.8 SD.

RESULTS

All 18 tests were performed without incident and were terminated as a result of volitional fatigue. Table 1 provides the mean peak rate pressure product (RPP), respiratory exchange ratio (RER), and rating of perceived exertion (RPE) for each testing condition. There was no difference between conditions for RPP and RPE. The RER was greater for T3.

Table 1. Peak exercise rate pressure product (RPP), respiratory exchange ratio (RER), and rating of perceived exertion (RPE).

Test	RPP	RER	RPE
T3	27,009±5200	1.15±0.08	17.5±1.4
T6	25,776±4642	1.05±0.07*	18.2±1.3

Values are mean±SD; n=9, except+n=7; T3 versus T6; *p = 0.0123

Peak work rate tended to be greater for T3 than for T6 (p=0.06), and as expected, the duration was longer for the T6 than the T3 test (Table 2). Plasma norepinephrine was greater at peak exercise for T3 than for T6 (Table 3). Despite this there was no significant difference in peak HR, or VO₂ (Table II) between the test protocols. HR reserve (peak HR minus rest HR) was also not different between the two test protocols: T3=52±7 b/min; T6=50±6 b/min.

Table 2. Time, work rate and VO₂ at peak exercise.

Test	Time (min)	Work Rate (Watts)	Oxygen Consumption (ml/min/kg)	(L/min)
T3	11.5±1.1	117±5	17.6±2.0	1.5±0.2
T6	8.8±2.1*	100±10**	17.4±1.9	1.5±0.1

Values are mean±SD; n=9; T3 versus T6; *p≤0.05, **p = 0.06

The 30 and 60 Watt work rates were used to compare the group mean submaximal responses between the T3 and T6 protocols. These were used because they were the only stages in which a majority of (i.e., n=8) subjects completed. At rest, and at the 30 and 60 Watt work rates there was no difference in plasma norepinephrine concentration and VO₂ between T3 and T6 (Table 3). HR was not different between T3 and T6 at rest or 30 Watts, but was higher at 60 Watts for T6 (Table 3).

The beta-receptor sensitivity index values are presented in table 4. Statistical analysis demonstrated no difference over time in either protocol (p=0.18) as exercise intensity increased. Additionally, there was no difference in beta-receptor sensitivity between the T3 and T6 tests (p=0.82).

DISCUSSION

Despite the predominant reliance of the decentralized heart on circulating catecholamines to increase heart rate during exercise (10, 11), the greater plasma norepinephrine concentration at peak exercise during T3 than during T6 did not result in a higher peak HR. The tendency toward a greater peak power output during T3 than T6 likely accounts for the higher peak plasma norepinephrine concentration observed during T3. It was somewhat surprising that the greater peak norepinephrine concentration occurred in the shorter duration stage test and that this had no influence on peak HR. However, this makes sense as this protocol (T3) resulted in a significantly greater peak work rate and a direct relationship between plasma norepinephrine concentration and work rate has been previously established (3).

A limitation of this study was the use of the subjective test endpoint of volitional fatigue. It might be argued that the lower peak work rate during T6 was the result of early peripheral fatigue occurring prior to the attainment of cardiorespiratory or metabolic limitation. This has been previously demonstrated in patients taking prednisone. The lower peak RER during T6 supports this notion. However, the mean RER for T6 was 1.05 and this can be considered a significant level of cardiorespiratory and metabolic demand. Due to the absence of research-based VO₂max or VO₂peak criteria for patients with a heart transplant, our lab uses RPP values above 25,000 and RPE levels above 17 as criteria for the attainment of maximal or near maximal levels of exertion. The mean of each of these variables for each testing condition was above these values and not different from each other.

Table 3. Heart rate, plasma norepinephrine and VO₂ at rest and during exercise.

Condition	Heart Rate (beat/min)		Nepi (pg/ml)		Oxygen Consumption (ml/min/kg)	
	T3	T6	T3	T6	T3	T6
<i>Rest</i>	91±1	92±1	700±120	627±72	3.0±0.4	3.2±0.8
<i>30 watts</i>	107±2	110±2	1523±284	1675±311	8.5±1.4	9.2±1.9
<i>60 watts+</i>	112±2	123±2*	1813±300	2150±428	11.3±2.7	12.7±2.1
<i>Peak</i>	143±2	142±1	3750±467*	3218±360	17.6±2.0	17.4±1.9

Values are mean±SD. T3 versus T6; n=9, except +n=8; *p=0.013; Nepi=plasma norepinephrine concentration

It is possible that the very high peak exercise norepinephrine concentration for both protocols, although different, may also account for the lack of difference in peak HR. This would occur if there is a norepinephrine saturation level, reached by the beta₁ receptors, at which point a further increase in norepinephrine concentration would be ineffective at producing a positive chronotropic response. The beta-receptor sensitivity index data supports this contention as there was no difference in beta-receptor sensitivity as exercise intensity increased; or between the shorter (T3) and longer (T6) exercise protocols at peak exercise intensity despite a difference in plasma norepinephrine concentration.

As a result of these findings, we conclude that an elevated plasma norepinephrine level has no effect on peak exercise heart rate in patients with a heart transplant. This absence of a greater peak HR, work rate, or VO₂ with an exercise protocol which uses 6 min incremental stages demonstrates that it is of limited value as a prescriptive technique for determining an appropriate training stimulus in a cardiac transplant patient. Previous studies involving patients with cardiac transplant have shown that peak HR increases after approximately 8 weeks of exercise training (7, 8), and also as a result of spontaneous recovery from surgery (12). Therefore, the progressive increase in peak HR in this patient population appears to be a chronic adaptation occurring during several weeks rather

Table 4. Beta-receptor sensitivity.

Work Level	T3	T6
<i>30 watts</i>	0.019±0.007	0.017±0.005
<i>60 watts</i>	0.023±0.013	0.020±0.005
<i>Peak Exercise</i>	0.017±0.006	0.019±0.001

Values are mean±SD; n=9; T3 versus T6

than an acutely manipulated response. However, this response is not likely to result in a higher VO_{2 peak} (6).

The results of this study indicate that during short-term exercise the work rate, and not duration, is

likely the most important determinant to the peak plasma norepinephrine concentration achieved. Another possibility is that it may take a work rate duration longer than three or six minutes to produce the necessary plasma norepinephrine concentration threshold to achieve an appropriate HR response. Anecdotal observation of cardiac transplant patients during exercise indicates that HR progressively rises during a 30 min aerobic exercise bout and this may be related to the longer (vs. 6 min) duration of elevated plasma catecholamine concentrations.

However, a higher acute, submaximal and peak HR response may not be possible in this patient population secondary to beta-receptor desensitization or a lack of direct sympathetic innervation.

Our findings differ somewhat from Olivari et al. (9), who recently reported a higher peak HR in the cardiac transplant patient during exercise in which work rate was increased only after a steady state VO₂ and HR response was observed. The higher peak HR occurred in conjunction with a significantly greater peak work rate and exercise duration. However, the authors also demonstrated no difference in peak VO₂, as we have shown. Norepinephrine concentration was not assessed. Interestingly, their subjects did not appear to be limited by local fatigue when the protocol stages were lengthened.

CONCLUSIONS

Given the absence of a difference between peak HR or HR reserve between the 3 min and 6 min stage tests, a longer stage duration protocol appears to be

of little clinical value. We suggest that the other accepted methods of exercise prescription, such as rating of perceived exertion, percent of maximal VO_2 , ventilatory threshold or lactate threshold, continue to be used to guide exercise intensity in patients with cardiac transplant.

REFERENCES

1. Allenmark, S., H. Hedman and A. Soderberg. Micro analysis of catecholamine in human plasma by high pressure liquid chromatographic separation. **Microchemical J** 1980;25:567-72.
2. Badenhop DT. The therapeutic role of exercise in patients with orthotopic heart transplantation. **Med Sci Sports Exerc** 1995;25:975-85.
3. Banner NR, Patel N, Cox AP, Patton HE, Lachno DR, Yacoub MH. Altered sympathoadrenal response to dynamic exercise in cardiac transplant recipients. **Cardiovascular Res** 1989;23:965-972.
4. Brubaker, P., M. Berry, S. Brozena, D. Morley, J. Walter, A. Paolone, et al. Relationship of lactate and ventilatory thresholds in cardiac transplant patients. **Med Sci Sports Exerc** 1992;25:191-6.
5. Ehrman, J., S. Keteyian, F. Fedel, K. Rhoads, B. Levine, R. Shepard. Ventilatory threshold after exercise training in orthotopic heart transplant recipients. **J Cardiopulm Rehabil** 1992;12:126-30.
6. Givertz M.M., Harley H., Colucci W.S. Long-term sequential changes in exercise capacity and chronotropic responsiveness after cardiac transplantation. **Circulation** 1997;96:232-237.
7. Kavanagh, T., M. Yacoub, D. Mertens, J. Kennedy, R. Campbell, P. Sawyer. Cardiorespiratory responses to exercise training after orthotopic cardiac transplantation. **Circulation** 1988;77:162-71.
8. Keteyian, S., J. Ehrman, F. Fedel and K. Rhoads. Heart rate - perceived exertion relationship during exercise in orthotopic heart transplant recipients. **J Cardiopulm Rehabil** 1990;10:287-293.
9. Olivari, M.T., C. W. Yancy, R.L. Rosenblatt. An individualized protocol is more accurate than a standard protocol for assessing exercise capacity after heart transplantation. **J Heart and Lung Transpl** 1996;15:1069-1074.
10. Pope, S.E., E.B. Stinson and G.T. Daughters. Exercise response of the denervated heart in long - term cardiac transplant recipients. **Am J Cardiol** 1980;46:213-218.
11. Quigg, R.J., M.B. Rocco, D.F. Gauthier, M.A. Creager, L.H. Hartley and W.S. Colucci. Mechanism of the attenuated heart rate response to exercise after orthotopic cardiac transplantation. **J Am Coll Cardiol** 1989;14:338-344.
12. Rudas, L., P.W. Pflugfelder, A.H. Menkis, R.J. Novick, F.N. McKenzie and W.J. Kostuk. Evolution of heart rate responsiveness after orthotopic cardiac transplantation. **Am J Cardiol** 1991;68:232-236.
13. Squires, R., P. Arthur, G. Gau, A. Muri, W. Lambert. Exercise after cardiac transplantation: a report of two cases. **J Cardiac Rehabil** 1983;35:570-574.

Address for Correspondence: Jonathan K. Ehrman, Ph.D., Henry Ford Health System, Division of Cardiology, Department of Internal Medicine, 6525 Second Ave., Detroit, MI 48202, Phone number: (313) 972-1689, email: Jehрман1@hfhs.org

Copyright © 1997-1999 American Society of Exercise Physiologists. All rights reserved.
