SUPPLEMENTAL MATERIAL

Exercise Training Regimen

Details of the exercise training regimen have been previously published[1] and a reproduced here for convenience. Exercise physiologists met with participants monthly throughout the intervention. The majority of monthly meetings were conducted in person. However, if this was not logistically possible, meetings were conducted electronically. During the initial training phase, exercise physiologists directly supervised many exercise sessions with the goal of educating participants about the different type of sessions and providing support and guidance to build self-confidence, develop self-efficacy to facilitate the independent completion of the exercise program. During monthly consults, exercise physiologists discussed the individual's progress, reviewed adherence to the intervention, and noted any issues (eg, musculoskeletal injuries, acute illness). The majority of exercise sessions throughout the training program were not supervised, although every session was carefully tracked using heart rate (HR) monitors.

To individualize training intensity, the maximal steady state (MSS) zone was obtained from ventilatory and lactate thresholds during the maximal exercise test.[2, 3] Based on MSS HR and peak HR (HR_{peak}), four training zones were established for each participant randomized to the exercise group: 1) MSS, 2) base pace (1-20 beats below MSS), 3) interval (>95% HR peak), and 4) recovery (<base pace). The early training phase (month 1–2) focused on establishing an endurance base and regular exercise routine with participants performing three, 30-minute base pace sessions per week. The majority of training in the early phase was base pace training. As participants acclimated to the training, MSS training was added, starting with 2 sessions per week

during the second month and increasing to 3 sessions per week in the third month. Thirty-minute strength training sessions were added twice per week to compliment aerobic exercise beginning during the second month. From the third month on, aerobic interval training consisting of “4 x 4” interval sessions (4 minutes of exercise at 95% HR_{peak} followed by 3 minutes of active recovery at 60-75% peak HR_{peak}, repeated four times) were incorporated.[4] A recovery day consisting of 20-30 minutes of walking followed each interval day to maximize performance gains. By the sixth month, participants were training 5-6 hours per week, including 2 aerobic intervals sessions, one long aerobic session (at least one hour), and one 30-minute base pace session each week. The dose of exercise was then maintained for an additional four months after which the 10-month peak training load testing was completed.

Following this peak training load, participants in the exercise group transitioned to a subsequent 14-month maintenance training phase. Training zones were adjusted to reflect the results of the most recent exercise test. During the maintenance period, participants performed 1 interval session per week plus continuous training. Participants were encouraged to use a variety of exercise equipment (eg, stationary cycle ergometer, treadmill, elliptical trainer) or perform exercise sessions outdoors (eg, running on trails, cycling, swimming) to ensure participant enjoyment and to avoid overuse injuries. To supplement the endurance training, 2 weekly strength training sessions designed to focus on core strength were prescribed. These sessions were designed to focus on whole body functional and core strength to complement the endurance training. After completion of the 24-month exercise regimen (10 months of

progressive training + 14 months of maintenance training), participants completed 24 month testing.

Exercise Testing

Measurements of maximal oxygen uptake were performed with a modified Astrand-Saltin protocol involving incremental exercise on a treadmill, at baseline, 10 months (after the peak training phase), and at 2 years by using the Douglas bag technique; gas fractions were analyzed by mass spectrometry, and ventilatory volumes were analyzed by a Tissot spirometer, as previously reported.[3] Maximal oxygen uptake (VO_2max) was defined as the highest oxygen uptake measured from at least a 30-second Douglas bag. At each testing session, VO_2, hemodynamics and blood pressures were determined at the following treadmill conditions: 1) quiet standing rest, 2) low-intensity (≈30—45% of VO_2max; SS1) steady-state submaximal exercise, 3) moderate-intensity (≈60—75% of VO_2max; SS2) steady-state 2 submaximal exercise, and 4) maximal exercise. Two participants were tested on an upright cycle at the same conditions because of orthopedic limitations. Gas fractions were analyzed by mass spectrometry and ventilatory volumes by a Tissot spirometer.[3] Maximal oxygen uptake (VO_2max) was defined as the highest oxygen uptake measured from at least a 30 second Douglas bag.

Echocardiographic Assessment:

3D images were obtained with a matrix array transducer and the dataset was transferred to Q-LAB (Phillips Medical Systems, Andover, USA) for offline analysis.[5, 6]

LA ESV was obtained by selecting the frame with the lowest volume within one beat of mitral valve closure. LA EDV was obtained by selecting the frame with the maximal volume up to one frame prior to mitral valve opening. LA ejection fraction (LA EF) was calculated using the following formula: LA EF = 100 x [(LA EDV – LA ESV)/LA EDV]. Pulsed wave Doppler was positioned at the tips of the mitral valve leaflets with a sample volume of 2.0 mm and was used to assess mitral inflow velocities.[7, 8] As in previous publications, we used the following formula to calculate the active emptying percentage of total LA emptying, where A_{VTI} represents active emptying during the atrial contractile phase, E_{VTI} + D_{VTI} represents passive emptying after mitral valve opening and atrial filling during diastasis time. LA Active Emptying % = [A_{VTI}/ (E_{VTI} + D_{VTI} + A_{VTI})]*100.[9]

Right Heart Catheterization:

Right heart catheterization was performed with a 6F Swan-Ganz catheter, which was placed under fluoroscopic guidance through an antecubital vein and advanced into the pulmonary artery. The wedge position of the catheter was confirmed by both fluoroscopy and the presence of typical waveforms. Mean pulmonary capillary wedge pressure (PCWP) and right atrial pressure were determined visually at end expiration using an electronic data measurement system (BIOPAC Systems Inc., Santa Barbara, CA).

References:

1. Howden EJ, Sarma S, Lawley JS, Opondo M, Cornwell W, Stoller D, Urey MA, Adams-Huet B and Levine BD. Reversing the Cardiac Effects of Sedentary Aging in Middle Age-A Randomized Controlled Trial: Implications For Heart Failure Prevention. *Circulation*. 2018;137:1549-1560.

2. Anderson GS and Rhodes EC. A review of blood lactate and ventilatory methods of detecting transition thresholds. *Sports Med*. 1989;8:43-55.

3. Arbab-Zadeh A, Perhonen M, Howden E, Peshock RM, Zhang R, Adams-Huet B, Haykowsky MJ and Levine BD. Cardiac remodeling in response to 1 year of intensive endurance training. *Circulation*. 2014;130:2152-61.

4. Simonsen T, Helgesen C, Hjorth N, Bach R and Hoff J. Aerobic high-intensity intervals improve VO2max more than moderate training. *Med Sci Sports Exerc*. 2007;39:665671.

5. Jenkins C, Bricknell K and Marwick TH. Use of real-time three-dimensional echocardiography to measure left atrial volume: comparison with other echocardiographic techniques. *J Am Soc Echocardiogr*. 2005;18:991-7.

6. Dorosz JL, Lezotte DC, Weitzenkamp DA, Allen LA and Salcedo EE. Performance of 3-dimensional echocardiography in measuring left ventricular volumes and ejection fraction: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2012;59:1799-808.

7. Cohen GI, Pietrolungo JF, Thomas JD and Klein AL. A practical guide to assessment of ventricular diastolic function using Doppler echocardiography. *J Am Coll Cardiol*. 1996;27:1753-60.

8. Prasad A, Popovic ZB, Arbab-Zadeh A, Fu Q, Palmer D, Dijk E, Greenberg NL, Garcia MJ, Thomas JD and Levine BD. The effects of aging and physical activity on Doppler measures of diastolic function. *Am J Cardiol*. 2007;99:1629-36.

9. Opondo MA, Aiad N, Cain MA, Sarma S, Howden E, Stoller DA, Ng J, van Rijckevorsel P, Hieda M, Tarumi T, Palmer MD and Levine BD. Does High-Intensity Endurance Training Increase the Risk of Atrial Fibrillation? A Longitudinal Study of Left Atrial Structure and Function. *Circ Arrhythm Electrophysiol*. 2018;11:e005598.