ELSEVIER

The Journal of
Heart and Lung
Transplantation

http://www.jhltonline.org

# High-intensity interval training in patients with cardiovascular diseases and heart transplantation

Carl J. Lavie, MD, FACC, FACP, FCCP,[a,b] Ross Arena, PhD,[c] and Conrad P. Earnest, PhD[d]

*From the [a]Department of Cardiovascular Diseases, John Ochsner Heart & Vascular Institute, Ochsner Clinical School–University of Queensland School of Medicine, New Orleans, Louisiana; [b]Department of Preventive Medicine, Pennington Biomedical Research Center, Louisiana State University System, Baton Rouge, Louisiana; [c]Department of Physical Therapy, College of Applied Health Sciences, University of Illinois Chicago, Chicago, Illinois; and the [d]Department for Health, University of Bath, Bath, UK.*

Substantial evidence supports the importance of physical activity (PA), exercise training (ET) and cardiorespiratory fitness (CRF) in patients with coronary heart disease (CHD) and heart failure (HF).[1–4] Certainly, ET has been demonstrated to markedly improve levels of CRF as measured by: 1) estimated exercise capacity or estimated metabolic equivalents (METs), determined typically by speed and incline on a treadmill or Watts on a cycle ergometer, 2) ventilatory expired gas that precisely quantifies peak oxygen consumption ($VO_{2peak}$) and 3) predictive modeling, and 4) simple testing such as the 6-minute walk test. In fact, cardiac rehabilitation and exercise training (CRET) programs, using moderate-intensity aerobic training as a cornerstone intervention, have been demonstrated to markedly improve estimated METs and $VO_{2peak}$, and these improvements correlate with reductions in morbidity and mortality in both CHD and HF.[1–4]

Not surprisingly, moderate-intensity ET has become part of the standard of care for most patients with cardiovascular diseases (CVD). Recently, however, evidence has emerged demonstrating that high-intensity interval training (HIIT) may be performed safely and results in improvements in physiology, functional capacity/CRF and quality of life (QoL), leading some to intimate that HIIT, as opposed to traditional moderate-intensity continuous training (MICT), should be the preferred clinical approach in patients with CVD.[5,6] In studies of patients with CHD and HF, as well as in cohorts of obesity and metabolic syndrome, HIIT has been typically superior to MICT for CRF, as determined by $VO_{2peak}$, and for positive adaptations in cardiac structure and function, including hemodynamics, biomarkers and various echocardiographic parameters.[5,6] This may be a somewhat controversial paradigm shift, particularly given the theoretical potential increases in adverse event risk associated with ET at higher intensities.

In patients undergoing heart transplantation (HT), there are also many potential benefits of ET, particularly on exercise capacity/CRF (e.g., $VO_{2peak}$ typically improves by nearly 25% after ET) and QoL.[7,8] The impact of ET on frequency or severity of acute rejection and survival has not been documented.[7] Clearly, ET has many theoretical and proven effects on patients with atherosclerosis,[2,3] but cardiac allograft vasculopathy (CAV) is a progressive form of atherosclerosis in HT recipients characterized by diffuse intimal thickening and more diffuse narrowing of small coronary arteries. This unique type of atherosclerosis is a major cause of morbidity and mortality in HT patients.[9,10] However, little is known about the impact of ET on CAV in patients undergoing HT.

In this issue, Nytrøen and colleagues[11] report that HIIT in HT patients resulted in a reduced rate of CAV progression during 1-year follow-up, suggesting that, in addition to statins and state-of-the art immunosuppressive therapy, HIIT could be included in the detailed treatment regimen for many HT recipients. Because CAV appears to be closely correlated with inflammation,[10] we may speculate that part of the ET benefit is via anti-inflammatory effects, which we have previously demonstrated.[12,13] However, HIIT only significantly lowered levels of interleukin-8,[11] and even this was not significantly different from the changes noted in a control group. Certainly, Nytrøen et al should be applauded for a well-conducted and interesting study with major potential clinical implications. However, numerous issues and questions exist that limit the immediate impact of their data.

First, the study population was relatively small ($N = 43$) and were divided between HIIT and standard care patients. Second, the study suggested benefits of HIIT on CAV progression by intravascular ultrasound (IVUS) criteria,

Reprint requests: Carl J. Lavie, MD, FACC, FACP, FCCP, Department of Cardiac Diseases, John Ochsner Heart and Vascular Institute, Ochsner Clinical School–University of Queensland School of Medicine, 1514 Jefferson Highway, New Orleans, LA 70121-2483. Telephone: 504-842-5874. Fax: 504-842-5875.

E-mail address: clavie@ochsner.org

1053-2498/$ - see front matter 
http://dx.doi.org/10.1016/j.healun.2013.08.001

which is impressive after only 1 year of treatment. However, it is not possible to determine whether the benefits were specifically related to HIIT or due to ET in general (e.g., would MICT have resulted in similar benefits?). Third, many of the IVUS parameters were numerically worse at baseline in the control group than in the HIIT group, raising concerns that, with respect to CAV, although not significantly different, the control group's CAV may have progressed more rapidly, a point that the authors countered by stating that the progression of CAV did not correlate with baseline IVUS parameters. Certainly, other statistical methods could have been used to analyze the changes in the 2 groups, but they too would have been limited by the relatively small number of patients. Finally, as admitted by Nytrøen et al, their patients had quite high levels of baseline CRF ($VO_{2peak}$ = 28 ml/kg/min), considerably higher than baseline values in most patients with CHD, HF and HT, which raises concerns about considerable selection bias in this unique cohort of HT recipients.

Regarding HIIT, their study data are consistent with findings from previous studies examining CHD and HF cohorts, suggesting that HIIT is safe even in patients with advanced CVD.[5,6] In our recent HF review,[6] only longer on/off cycles (e.g., 3 minutes on and 3-minute recovery) seemed to produce better improvements in $VO_{2peak}$ than MICT, whereas shorter on/off cycles (e.g., 30 to 90 seconds) produced results more comparable to those of HIIT and MICT. Nevertheless, in our review of the world's literature on HIIT and HF, we analyzed data in just over 100 patients, demonstrating the major problem in advocating for routine implementation of HIIT in current clinical practice—that is, the current total body of literature examining this ET approach has examined a limited number of patients. In the Nytrøen et al study,[11] the ET protocol utilized 4 minutes of HIIT/3 minutes of active recovery, where ET was performed at approximately 90% of maximal heart rate. Certainly, more data are needed on the optimal type of HIIT in many patients with CVD, including those with CHD, HF and HT. In most of these patients the long-term efficacy and safety of HIIT still needs to be demonstrated above and beyond the benefits obtained with MICT, including that for CAV in HT patients. In addition, HIIT needs to be studied intermixed with MICT, which is the ET method of choice used in the majority of rehabilitation programs, including those frequently utilized by competitive athletes.

At present, HIIT seems to be showing considerably greater promise with each published study. Among many exercise physiologists, ET clinicians and scientists, there seems to be a growing consensus that HIIT produces greater benefits than MICT. However, despite the potential benefits of HIIT above and beyond that of MICT, there have been no studies on CHD, HF or HT demonstrating benefits in major clinical morbidity and mortality with HIIT. A new randomized, multicenter trial (SMARTEX-HF) in Europe will begin to address many of the questions requiring further attention with HIIT.[14] SMARTEX-HF will include 200 subjects with systolic HF and randomize them to one of the following groups: (1) 12-week supervised HIIT; (2) 12-week supervised MICT; or (3) education on how to perform an independent ET program. Left ventricular remodeling, exercise performance, B-type natriuretic peptide and QoL will be assessed immediately after (i.e., 12 weeks) the intervention, as well as at 1 year. Subjects in this study will also be tracked for ET compliance, ET-related adverse events and overall morbidity and mortality. However, HT is mostly a model of diastolic HF, with elevated filling pressures at rest and with exercise, presumably due to hypertension, acute rejection episodes resulting in myocardial scarring and fibrosis, as well as CAV[7]; SMARTEX-HF, on the other hand, will study systolic HF.

In general, ET presents a challenge in HT patients, where the transplanted heart is surgically denervated and receives no direct efferent input and provides no direct afferent signals to the central nervous system.[7] As a result of loss of parasympathetic innervation of the donor heart, heart rate (HR) at rest is elevated to approximately 95 to 115 beats/min and represents the inherent rate of depolarization of the sino-atrial node. With graded ET, HR does not typically increase for several minutes, followed by a gradual rise with peak HR to generally lower than normal (typically as high as 150 beats/min, but often in the low- to mid-130s range) due to sympathetic nervous system denervation. In fact, many HT patients achieve their highest HR during the first few minutes of recovery, before gradually returning to their resting HR (with delayed HR recovery). Therefore, regulation of HR during ET in HT patients is almost totally dependent on circulating catecholamines. However, several months or years post-HT, many HT patients develop partial cardiac sympathetic efferent reinnervation, which is associated with partial "normalization" of a typical HR response and higher maximal HR (e.g., HR in the high 140s instead of mid-130s), and this is associated with improved overall exercise capacity.[7,8,15]

The prescribed ET for HT patients is similar to that for other cardiac patients,[2,3] with the one exception that target HR is not used, unless the HT patient exhibits a partially normalized HR response to ET, as described previously.[7] A Borg Perceived Exertion Scale score of 12 to 14 (described as "somewhat hard") may be used to prescribe ET intensity, and the ET prescription should include standard warm-up and cool-down, a gradual increase in aerobic ET duration to 30 to 45 minutes, with a frequency of 4 to 6 sessions/week. If cardiopulmonary stress testing is available, which would be ideal for prescribing a detailed ET regimen, this would be utilized as described by Nytrøen et al,[11] depending on whether MICT, HIIT or some combination is utilized. Typical aerobic ET involves walking (treadmill and outdoor), elliptical machines, cycle ergometry and stair climbing. In addition, skeletal muscle weakness is extremely common in HT recipients, due to skeletal muscle atrophy with advanced HF, pre-HT deconditioning and post-HT use of corticosteroids and other immunosuppressant agents. As in other cardiac patients, muscle strength is also very important,[16] so muscle-strengthening ET, or resistance ET, is also needed to counter these factors. This resistance ET should emphasize moderate resistance, 10 to 20 slow repetitions per set and 1 to 3 sets of resistance ET for the major muscle groups, with a frequency of 2 or 3 sessions per

week, again using an intensity of 12 to 14 on the Borg Scale to gauge the intensity of lifting.

Although the Nytrøen et al[11] study is intriguing, larger studies with a longer follow-up and clinical end-points, such as the SMARTEX-HF trial,[14] are needed before HIIT becomes routinely utilized in HF patients, much less HT patients. Finally, regardless of the type of ET utilized (MICT, HIIT with various on/off cycles, and various combinations of these modalities), greater efforts are needed to promote PA, ET and improvements of CRF for the general population (primary prevention)[1,2] and for patients with CVD (secondary prevention).[1–8,12,13,17] Specifically, in secondary prevention, efforts are needed to improve referral and attendance of patients with CVD in formal CRET programs, which has been the case for decades in patients with CHD,[2,3,17] and now should be extended to those with HF[4,6] and HT.[7,8,11]

## Disclosure statement

The authors have no conflicts of interests to disclose.

## References


1. Kaminsky LA, Arena R, Beckie TM, et al. The importance of cardiorespiratory fitness in the United States: the need for a national registry: a policy statement from the American Heart Association. Circulation 2013;127:652-62.
2. Swift DL, Lavie CJ, Johannsen NM, et al. Physical activity, cardiorespiratory fitness, and exercise training in primary and secondary coronary prevention. Circ J 2013;77:281-92.
3. Lavie CJ, Milani RV. Cardiac rehabilitation and exercise training in secondary coronary heart disease prevention. Prog Cardiovasc Dis 2011;53:397-403.
4. Lavie CJ, Berra K, Arena R. Formal cardiac rehabilitation and exercise training programs in heart failure: evidence for substantial clinical benefits. J Cardiopulm Rehabil Prev 2013;33:209-11.
5. Kemi OJ, Wisloff U. High-intensity aerobic exercise training improves the heart and health in disease. J Cardiopulm Rehabil Prev 2010;30:2-11.
6. Arena R, Myers J, Forman DE, et al. Should high-intensity-aerobic interval training become the clinical standard in heart failure? Heart Fail Rev 2013;18:95-105.
7. Squires RW. Exercise training in cardiac transplant recipients. Prog Cardiovasc Dis 2011;53:429-36.
8. Kobashigawa JA, Leaf DA, Lee N, et al. A controlled trial of exercise rehabilitation after heart transplantation. N Engl J Med 1999;340:272-7: ([erratum: 1999;340:976]).
9. Mehra MR, Crespo-Leiro MG, Dipchand A, et al. International Society of Heart and Lung Transplantation working formulation of a standardized nomenclature for cardiac allograft vasculopathy—2010. J Heart Lung Transplant 2010;29:717-27.
10. Ventura HO, Mehra MR. C-Reactive protein and cardiac allograft vasculopathy: is inflammation the critical link? J Am Coll Cardiol 2003;42:483-5.
11. Nytrøen K, Rustad LA, Erikstad I, et al. Effect of high-intensity interval training on progression of cardiac allograft vasculopathy. J Heart Lung Transplant 2013;32:1073-80.
12. Milani RV, Lavie CJ, Mehra MR. Reduction in C-reactive protein through cardiac rehabilitation and exercise training. J Am Coll Cardiol 2004;43:1051-61.
13. Lavie CJ, Church TS, Milani RV, et al. Impact of physical activity, cardiorespiratory fitness, and exercise training on markers of inflammation. J Cardiopulm Rehabil Prev 2011;31:137-45.
14. Støylen A, Conraads V, Halle M, et al. Controlled study of myocardial recovery after interval training in heart failure: SMARTEX-HF-rationale and design. Eur J Cardiol 2012;19:813-21.
15. Bengel FM, Ueberfuhr P, Schiepel N, et al. Effect of sympathetic reinnervation on cardiac performance after heart transplantation. N Engl J Med 2001;345:731-8.
16. Artero EG, Lee DC, Lavie CJ, et al. Effect of muscular strength on cardiovascular risk factors and prognosis. J Cardiopulm Rehabil Prev 2012;32:351-8.
17. Balady GJ, Ades PA, Bittner VA, et al. Referral, enrollment, and delivery of cardiac rehabilitation/secondary prevention programs at clinical centers and beyond: a presidential advisory from the American Heart Association. Circulation 2011;124:2951-60.