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Upper Limits of Aerobic Power and Performance in Heart Transplant Recipients: Legacy Effect of Prior Endurance Training

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December 3rd, 2017 marks the 50th anniversary of the first human-to-human heart transplant (HT) surgery performed by Dr. Christiaan Barnard at the Groote Schuur Hospital in Capetown, South Africa. Since this seminal operation, over 124,000 heart transplants have been performed, and the survival rate has improved significantly (current median survival: 11.9 years) as a result of refinements in donor and recipient selection, advances in surgical techniques, organ preservation strategies, and immunosuppressive therapy.

Despite improvement or normalization of left ventricular systolic function, heart transplant recipients (HTR's) typically have a peak aerobic power (peak $\dot{V}O_2$) that is ≈40% lower than age and activity-matched healthy people.[1] Persistent impairment of peak $\dot{V}O_2$ following HT is multifactorial with contributions from abnormal skeletal muscle function associated with pre-HT heart failure (HF), bedrest deconditioning associated with prolonged hospitalization, post-transplant cardiac allograft denervation, and immunosuppression therapy.[1]

Although short-term (<12 months) exercise training among HTR's is an effective therapy to increase exercise capacity, peak $\dot{V}O_2$ typically remains ≈20% lower than values seen in healthy, normally active age-matched people. However, not all HTR's remain permanently

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impaired and mounting experience suggests that some patients are capable of performing high levels of physical activity following HT. We previously reported the athletic ability of a man who was normally active prior to the development of non-ischemic cardiomyopathy, underwent successful HT at age 26, and then began performing moderate to high-intensity endurance exercise training 18 years post-HT (45 years of age) culminating in completion of an Ironman triathlon (first HTR to complete an Ironman race) and the Boston marathon at 22 and 27.7 years post-HT, respectively.[2, 3] Notably, his peak $\dot{V}O_2$ value measured in close proximity to the Ironman triathlon was similar to that of age-matched male endurance athletes. More recently (31 years post-HT), his average heart rate recorded during a 10km training run was 138 bpm (85% age-predicted maximal heart rate). This experience suggests intact plasticity of the post-HT cardiovascular system which enables training adaptation and thereby the capacity to safely perform extreme endurance exercise 2 to 3 decades post-HT.

More recently, our group has had several unique opportunities that suggest a fitness "*legacy effect*" among HTR's. Specifically, we report our collective experience working with two highly trained endurance athletes who developed end-stage HF necessitating HT and then regained high levels of aerobic power and athletic capability following successful HT.

The first individual's HT surgery was performed in 2012 when he was 40 years of age.[4] Prior to developing HF due to non-ischemic cardiomyopathy, he completed 6 ironman duration races over 6 years (2-months prior to the onset of HF his peak $\dot{V}O_2$ = 46 ml/kg/min).[4] During the 13-month period after HF diagnosis, his peak $\dot{V}O_2$ decreased to 9 ml/kg/min, followed shortly thereafter by a period of prolonged bed rest (179 days) before HT. He began stationary cycling 2 weeks after HT and then resumed structured endurance training 8-months later. Since October 2013 he has competed in over 60 endurance races including multiple Ironman triathlons (n=3, including the Ironman world championship race, the first HTR to finish this event), the Transalpine run (7 days, 257 Km, total ascent/descent: 28,582m; race time: 46.4 hours; mean HR: 133 bpm), Cape Epic mountain bike race (8 days, 654 km, total climbing: 14,550m; race time: 45 hours; mean HR:136 bpm), Bike Transalp (7 days, 537 Km, total ascent/descent:16,820 m; race time: 33.7 hours; mean HR: 138 bpm) and the Ötztaler Bike Marathon (238km, 5,500 climbing meters, race time: 11.5 hours, mean HR: 136 bpm).

The second individual's heart transplant surgery was performed in 2014 when he was 24 years of age. He had previously been a professional cyclist (peak $\dot{V}O_2$: 71-75 ml/kg/min) until he suffered a non-specific viral illness complicated by a non-ischemic cardiomyopathy and severe HF. Following extended duration (4 months) BiVAD therapy he underwent successful HT. He began performing stationary cycling 10 days post-HT after which he gradually escalated his exercise regimen over the ensuing year. He performed a cardiopulmonary exercise test 14-months post-transplant, and then resumed a training regimen typical for a competitive cyclist including high volume and intensity training in close consultation with one of the authors (ALB).

HTR's, including the two patients described above, achieve their greatest improvement in peak $\dot{V}O_2$ during the first post-operative year. Notably however, both individuals we report

continued to experience significant increases in peak $\dot{V}O_2$ over a more extended period of time (Figure 1 A&B). To our knowledge, the pre-to-post-HT improvement in peak $\dot{V}O_2$ (6.2-fold increase, delta change: 47 ml/kg/min) for the HTR triathlete and the peak $\dot{V}O_2$ (64 ml/kg/min) for the HTR cyclist are the highest ever reported values among this patient population. Moreover, their post-HTR peak VO_2's were 122% (HTR triathlete) and 85-90% (HTR cyclist) of their pre-HF peak $\dot{V}O_2$'s when they were highly trained endurance athletes. The latter finding is remarkable given the professional cyclist's peak $\dot{V}O_2$ when he was competing at an elite level was 71 to 75 ml/kg/min. Finally, the highest peak $\dot{V}O_2$'s of our endurance trained HTR is 2.7 to 3-fold higher than that reported for 1,700 HTR's.[1]

Mechanisms underlying post-HT increases in peak $\dot{V}O_2$ include functional sympathetic reinnervation of the cardiac allograft (e.g. heart rate [HR] increase >60 bpm with exercise and immediate decrease in HR after exercise). HR data derived from serial cardiopulmonary exercise testing of our HTR cyclist illustrate this phenomenon. During an 18-month time period which involved 6 sequential tests, maximal HR fluctuated between 169 and 179 bpm, resting HR decreased by 10 to 22 bpm, and 2-minute recovery HR increased by 16 bpm. Although beyond the scope of this report, concomitant exercise-induced adaptations in cardiac, peripheral vascular, and skeletal muscle function contributed to his steady fitness gains. Specifically, our HTR cyclist peak and reserve (peak minus rest) HR is similar to that reported by Pokan et al. for 12 male HTR endurance athletes who performed high volume and intensity training (mean peak $\dot{V}O_2$: 45.2 ml/kg/min, all with evidence of cardiac reinnervation).[5] Notably, his peak $\dot{V}O_2$ over a 32-month period post-transplant was nearly 30% higher than that reported by Pokan et al (Figure 1B). In accordance with the Fick principle, the superior peak $\dot{V}O_2$ is the result of a greater peak exercise stroke volume and/or oxygen extraction (likely due to favorable vascular function, skeletal muscle capillarity and mitochondrial oxidative capacity) associated with long-term endurance training prior to and after transplantation.

In summary, the HTR athletes highlighted in this *Perspective* serve as inspiring examples of the remarkable human performance capacity that can be realized when conventional post-HT multi-disciplinary medical therapy is coupled with carefully monitored endurance exercise training. Moreover, they highlight the potential of a *'legacy effect'* by which high pre-HT levels of aerobic fitness may dictate trainability and exercise capacity following successful transplantation surgery.

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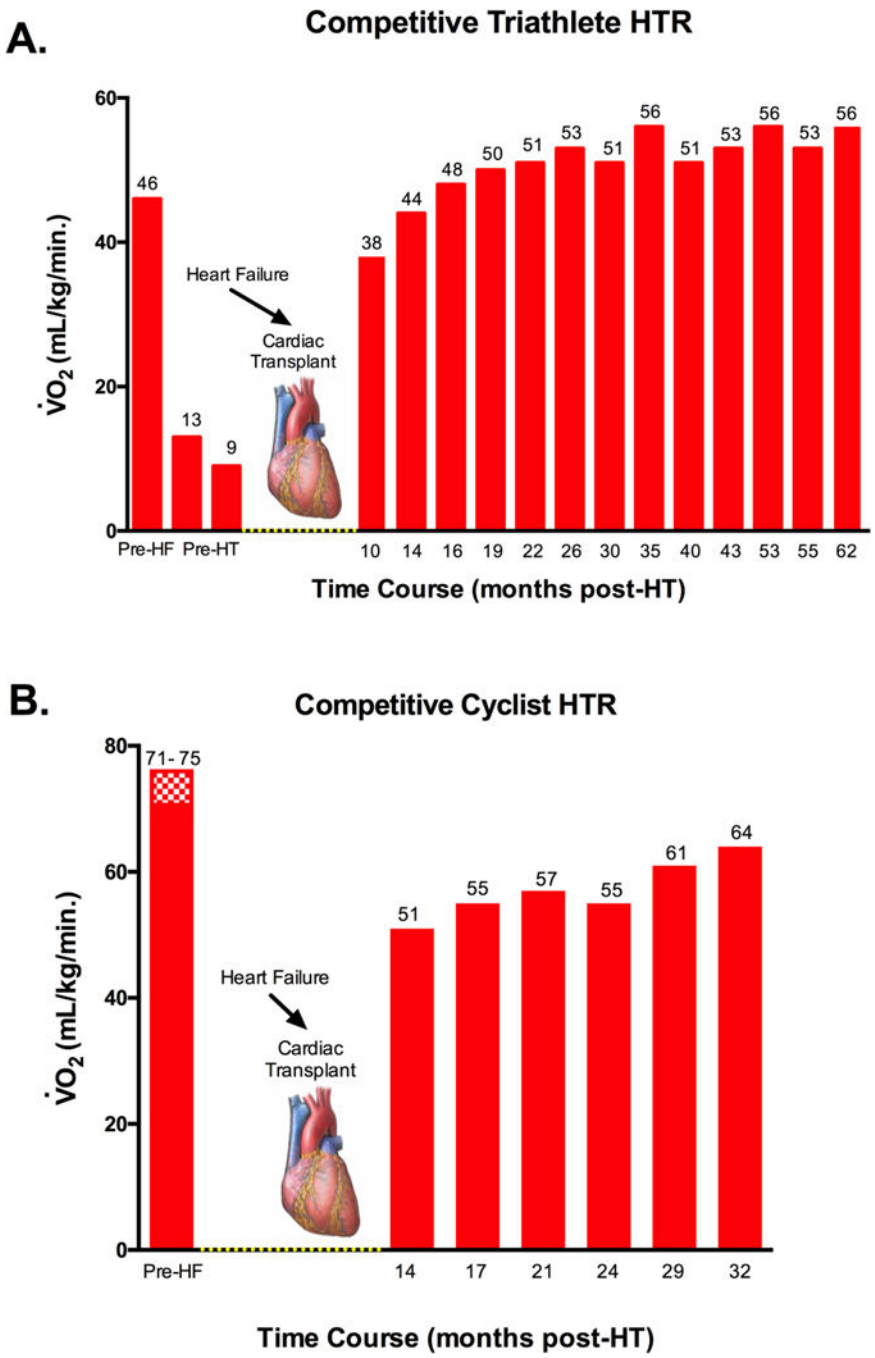

Figure 1.

Data derived from serial cardiopulmonary exercise testing performed in a prior endurance trained triathlete (A) and professional cyclist (B) who underwent heart transplantation (HT).