Is there a correlation between documented graft reinnervation and physiological improvements in response to exercise, underlining the major role of an intact autonomous nervous system during strenuous activity? Indeed, two studies report improved functional parameters of exercise testing. Evaluated up to 13.4 yr postoperatively, positron emission tomographic (PET) evidence of reinnervation was found in 80% of patients more than 3 yr after HTx, with better peak VO2 values than those without signs of reinnervation (27). Bengel et al. (3) added radionuclide angiography to PET examinations and demonstrated sympathetic reinnervation mainly in the anteroseptal wall in 16 of 29 patients with a mean follow-up of 3.2 yr after HTx. Reinnervated patients had a significantly longer exercise time and higher peak heart rate compared with those without denervation. Furthermore, the contractile response to exercise was significantly enhanced in the former group. Although workload and maximal heart rate reached levels that did not differ significantly from controls in this study, reinnervation is incomplete and with a broad individual spread, perhaps explaining why not all follow-up studies are able to pick up improvements in heart rate and peak VO2 over time (8).

In summary, the persistent impairment in exercise capacity after HTx relates strongly to a combination of chronotropic and inotropic incompetence, both consequences of cardiac denervation. Evidence of late partial reinnervation in some patients, coupled with improved physical capacity, underlines the importance of an intact functioning autonomic nervous system to maintain a normal circulatory response to exercise also in HTx recipients.

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dysfunctions) and peripheral (endothelial and muscular impairments) mechanisms have been proposed to explain such reduced exercise capacity (2, 8, 17, 18, 21). Although Htx often present with preserved cardiac (lusitropic and inotropic) and pulmonary functions, surgery-induced cardiac denervation deserve to be discussed.

Indeed, vagal tone withdrawal increases the resting heart rate (HR), leading to a chronotropic incompetence mainly characterized by a reduced heart rate reserve (HRR) during exercise. Although correlation does not imply causation, the relationship between the chronotropic response and peak oxygen consumption ($\dot{V}O_2$; Refs. 12, 21) suggests that cardiac denervation might play a key role in exercise limitation after heart transplantation. Thus reduced HRR was significantly correlated with reduced maximal $\dot{V}O_2$ in both sedentary (12) and highly (21) trained Htx patients. However, an elevated intensity might be necessary to reveal the central limitation of exercise capacity after heart transplantation (21) and the improvement of the heart rate response is not readily associated with an increase of the subject maximal $\dot{V}O_2$. Accordingly, Marconi et al. (15) demonstrated that, despite reacquiring a normal HR response to exercise both in terms of kinetics and maximal level, pediatric Htx patients showed impaired kinetics of $\dot{V}O_2$ on-response and a reduced maximal aerobic power. Similarly, the one-third of Htx patients normalizing their HR response to graded exercise 1 yr after transplantation still presented with a reduced aerobic capacity, despite their higher peak HR response and larger HRR (26). Finally, when the heart is artificially accelerated by rate-responsive pacing, the improvement on both peak heart rate and exercise capacity is small, not observed, or unnecessary (3, 28, 25).

These results are not unexpected since it is well known that the central oxygen transport remains adequate during exercise after heart transplantation. Indeed, in Htx, the reduction in HR increase is compensated by a simultaneous increase in stroke volume. Furthermore, the increased stroke volume is partly due to an increased venous return, leading to an enhanced cardiac peptide release. Such vasodilator peptide hypersecretion might be a compensatory mechanism allowing for improved blood flow and, therefore, $O_2$ redistribution during exercise (6, 10, 11, 16, 19).

We are now talking about the major limitations of exercise capacity after heart transplantation, i.e., endothelial and muscular limitations. Concerning blood flow and $O_2$ distribution to skeletal muscle, several studies demonstrated a decrease in the extent of the muscle capillary network in Htx (13, 24). Furthermore, global vascular dysfunction, related or not to the immunosuppressive therapy, has been well documented after heart transplantation. Of particular importance is the endothelium, which plays a pivotal role in redistributing blood flow during exercise through vasomotor factor secretion. Endothelial dysfunction has been consistently reported after heart transplantation, characterized by a decreased NO bioavailability and an increased endothelin-1 synthesis and characterized by an impaired flow-mediated dilatation (1, 7, 9). During exercise, unlike healthy subjects, Htx demonstrated a reduced NO secretion that was associated with their reduced exercise capacity (23). Furthermore, the decreased flow-mediated dilatation observed after heart transplantation has been associated with their exercise capacity. Finally, the beneficial effect of exercise training on exercise capacity has been related to an improvement in Htx endothelial function, the patients’ HRR remaining largely unmodified. Thus, clearly, endothelial dysfunction importantly participates in exercise capacity limitation after heart transplantation. Such a mechanism, through the generation of a relative muscular hypoxemia, leads also to the second main factor explaining Htx reduced exercise capacity, i.e., the muscular dysfunction.

Several authors point out that skeletal muscle metabolic abnormalities are the major cause of Htx limited exercise capacity. Indeed, an increased phosphocreatine breakdown for a given work rate and a decreased ATP resynthesis rate has been observed in these patients (27). Compared with control subjects, together with functional capacity, the muscle leg strength is also lowered after transplantation, and, in the absence of regular physical activity, this deficit will persist for a long time after transplantation (5, 24). Interestingly, this limitation remains reversible by training, and the ultrastructural mitochondrial volume density of the vastus lateralis muscle as well as the mitochondrial respiration and the energy transfer systems quantitatively and qualitatively respond to physical training, up to values previously measured in healthy, trained subjects (14, 29, 30). Accordingly, after rehabilitation, lower lactate values are observed for a similar mechanical power, also showing that the central convection (i.e., HR and cardiac output responses) is adapted to the muscle oxygen request (14, 20).

Thus four arguments strongly support that cardiac denervation does not play a key role in exercise limitation after heart transplantation.

1) If there is a clear relationship between heart rate response and peak $\dot{V}O_2$ in heart transplant patients, correlation does not imply causation and the directing factor is muscular energetic requirement and not $\dot{V}O_2$ convection.

2) Accordingly, spontaneous or artificial enhancement of the heart rate response is not associated with a proportional increase of peak $\dot{V}O_2$ after heart transplantation.

3) Vascular factors such as endothelial dysfunction importantly participate in exercise capacity limitation after heart transplantation and training-induced improvement in endothelial function leads to improvements in exercise capacity.

4) Finally, heart transplant patients present with skeletal muscles abnormalities, the main “effector” of exercise, and, like vascular alterations, muscular impairments can be reversed, allowing for significantly improved Htx exercise capacity.

Taken together, these data strongly support that an impaired HRR due to cardiac denervation is not the principal factor determining Htx functional capacity. This should not be surprising since it is well known that the oxygen demand in muscular tissues is the main driving factor of cardiorespiratory adjustments during exercise (and not the opposite). Thus we should focus directly on peripheral function (vascular and muscular) rather than on the central mechanisms of oxygen transport to reverse the exercise capacity limitation observed after heart transplantation.

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REBUTTLA FROM DR. ANDREASSEN

Richard, Zoll, Mettauer, Piquard, and Geny focus on the periphery in their discussion—are their arguments and references central in explaining the diminished exercise capacity among HTX recipients? I think not and will address the evidence for the four main arguments put forward.

1) While correlation may not necessarily translate into causation, the larger referred studies have sufficient power to allow robust statistical analysis (2, 3, 6). Multiple regression analysis in each of these studies confirms that peak heart rate and heart rate increase are powerful independent predictors of exercise capacity. Furthermore, invasive studies show that a reduced heart rate response is not compensated by an increase in stroke volume during exercise in HTx recipients (4), underlining that denervation may lead to both chronotropic and inotropic incompetence.

2) Braith et al. (1) demonstrated a higher peak heart rate with a parallel significant improvement of peak VO2 of 22% in HTX recipients receiving chronotropic support with a rate-responsive pacemaker. Pacing of the allograft in synchrony with the intrinsic depolarization rate of the native SA node may not be coupled to the dynamic metabolic demands of exercise, perhaps explaining why another study could not confirm the same benefit (9). In the absence of larger trials using chronotropic support, the issue of possible beneficial effects of exercise