Point: Counterpoint: Cardiac denervation does does not play a major role in exercise limitation after heart transplantation

**Point: Cardiac Denervation Does Play a Major Role in Exercise Limitation After Heart Transplantation**

With more than 100,000 procedures performed worldwide, more than 50% of patients undergoing orthotopic heart transplantation (HTx) survive longer than 10 years and enjoy significant and lasting improvements in their quality of life. However, exercise capacity by objective exercise testing has been shown to be markedly reduced. Despite normal ventricular ejection fraction at rest and a peak oxygen consumption that is higher than compared with preoperative values, exercise performance is typically only 40–60% of age-, sex-, and weight-matched controls. This phenomenon is best explained by the consequences of cardiac denervation at the time of explantation of a donor heart with subsequent HTx.

In nontransplanted subjects, the capacity for performing aerobic exercise depends on the ability of the heart to augment its output to exercising muscles and the ability of these muscles to use oxygen from the delivered blood. The increase in cardiac output (typically 4- to 6-fold) is caused by tachycardia operating in concert with increased myocardial contractility (20–50% augmentation of stroke volume) brought about by the greater sympathetic activity, together with the Frank-Starling mechanism (1). The autonomic nervous system plays a key role in the regulation of heart rate. The initial rise in heart rate is due to withdrawal of vagal tone, resulting in an increase of 30–50 beats/min. Thereafter, increments are attributed to an increase in activity to cardiac sympathetic nerves (20).

HTx recipients modulate their cardiac output in response to exercise in a different manner than in the normal heart, with no direct parasympathetic or sympathetic innervation. Due to lack of effenter vagal control, resting heart rate is elevated and with limited ability to increase heart rate early in exercise. Thus initial increases in cardiac output are completely dependent on augmented stroke volume (18). Increases in heart rate during later phases of exercise rely on an increase in circulating catecholamines because of sympathetic denervation (18). Importantly, the expected maximal inotropic left ventricular stimulation may also suffer from denervation due to at least two mechanisms. First, intact sympathetic nerve terminals with local norepinephrine release are required for maximum ventricular inotropic stimulation (20). Second, according to the frequency-force relationship, the time interval between beats is a determinant of the force of myocardial contraction. While the background for this last phenomenon is uncertain, it has been linked with calcium availability to contractile elements (4).

Several reports have demonstrated an association between subnormal exercise capacity and chronotropic incompetence in the form of reductions in the rate of rise in heart rate, increase in heart rate, and peak exercise heart rate (2, 5, 8–10, 14, 15, 19, 21, 22, 26). The largest studies have also shown that heart rate is a powerful and independent predictor of exercise capacity (8, 9, 14). Assessing maximal symptom-limited graded upright bicycle testing with simultaneous invasive hemodynamic monitoring, Kao et al. (10) described the consequences of a 30% lower heart rate response and 79% lower heart rate reserve in 30 HTx recipients compared with healthy controls. The lower stroke and cardiac index throughout exercise, coupled with inability to compensate with the Starling mechanism, resulted in 43% lower peak weight-adjusted oxygen consumption than in controls. The authors conclude that the chronotropic incompetence “is no doubt a result of the effects of denervation” and a major limiting factor to exercise capacity. The lack of direct innervation of the sinoatrial node as the cause for the attenuated response to peak heart rate to exercise in HTx is strongly supported by the observations that the rise in circulating catecholamines is normal or increased at peak exercise, and the responsiveness of the sinoatrial node to beta-adrenergic stimulation is also normal or increased (7, 23).

Serial assessment of exercise capacity in HTx recipients demonstrates some improvement in heart rate and peak VO2 during the first postoperative year (9). Nevertheless, they remain less fit at 1 year also compared with patients undergoing coronary artery bypass graft surgery (23). Interestingly, when extending comparisons to renal transplant recipients without denervated hearts, a near-normal exercise capacity is reached within a few months after surgery (6). The latter observation shows that contrary to speculations, the use of standard immunosuppressive medication does not necessarily relate to below-normal exercise capacity. Furthermore, while regular exercise and rehabilitation can improve peak VO2 and workload in various patient groups, improvements in heart rate reserve and peak heart rate in HTx recipients are either modest or negligible. In the mentioned comparison with bypass-treated patients, heart rate reserve was unchanged among HTx recipients while it increased significantly in the former group (16). In the only controlled trial of postoperative rehabilitation after HTx, Kobashigawa et al. (13) demonstrated a 2.5 ml·kg⁻¹·min⁻¹ higher increase in peak VO2 after 6 mo in the exercise group than in the nonexercising group without any difference in improvement of peak heart rate at the end of the study. Thus, whereas exercise training within the first year after HTx modestly increases the capacity for physical work compared with a more sedentary daily life, this must either be due to a physiological training effect such as improved muscle-skeletal weakness or merely an ability to exercise with greater effort.

Although conflicting results have been obtained, some studies describe the abnormal chronotropic response to exercise initially after HTx to return toward normal after 1–2 yr, suggesting sympathetic reinnervation (9, 21). Conclusively observed in animals (12), reinnervation in humans has also been inferred from invasive measurements of transcardiac epinephrine spillover (26), noninvasive imaging with radiolabeled catecholamine analogs (24), and by heart rate variability analyses (11), supported by observations such as typical anginal pain in those with graft vasculopathy (25) and regrowth of nerves across the aortic anastomosis determined by microscopy (17). Taken together, experimental and clinical evidence suggests that some degree of sympathetic reinnervation takes place over time at the sinus and the ventricular level, but not in all patients.

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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 VO_{2} 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 with 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 VO_{2} 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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COUNTERPOINT: CARDIAC DENERVATION DOES NOT PLAY A MAJOR ROLE IN EXERCISE LIMITATION AFTER HEART TRANSPLANTATION

Despite a successful replacement of the failing heart, heart transplant recipients (Htx) generally demonstrate persistent exercise capacity limitations compared with matched sedentary subjects (4, 16, 22). Both central (cardiac and pulmonary
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 (V\textsuperscript{\textcircled{O2}}; 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 V\textsuperscript{\textcircled{O2}} 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 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 V\textsuperscript{\textcircled{O2}}. 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 V\textsuperscript{\textcircled{O2}} 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\textsubscript{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\textsubscript{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 V\textsuperscript{\textcircled{O2}} in heart transplant patients, correlation does not imply causation and the directing factor is muscular energetic requirement and not V\textsuperscript{\textcircled{O2}} convection.

2) Accordingly, spontaneous or artificial enhancement of the heart rate response is not associated with a proportional increase of peak V\textsuperscript{\textcircled{O2}} 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 focalize 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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REBUTTAL 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 $V_{O_2}$ of 22% in HTx recipients receiving chronotropic support with a rate-responsive pacemaker. Facing 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...
capacity by artificial enhancement of heart rate may seem unanswered.

3) I am grateful to my opponents’ contribution to improving my citation index, but other vasoactive studies should also be mentioned in search of evidence for endothelial dysfunction in HTx recipients. Sinoway et al. (8) described a delayed reversal of impaired vasodilation after HTx and Kubo et al. (5) found normal forearm blood flow responses to an endothelium-dependent agent within 4 mo. Thus no consensus exists on maintained impaired endothelium-dependent vasodilation after HTx. In fact, postoperative normalization is described in studies where well established methods for evaluation of vasodilator responses have been used. Also, I am unaware of any studies assessing the effect of training on peripheral blood flow.

4) After describing various skeletal muscle metabolic abnormalities, Richard et al. (7) state that these limitations are reversible after training to levels comparable with controls. Considering that peripheral structural microangiopathy and minimal vascular resistance do gradually normalize within the first year (10), which peripheral factors could then explain why most HTx recipients with or without training, continue to demonstrate subnormal exercise capacity, if not taking central factors as denervation into account?

REFERENCES


REBUTTAL FROM DDS. RICHARD, ZOLL, METTUAERA, PIQUARD, AND GENY

First, even if surprising to the readers, we will agree with many of Dr. Andreassen’s statements (1). Particularly knowing that his team demonstrated that “peripheral factors, such as vasoreactivity and increased minimal resistance, are related to exercise performance after heart transplantation” (6), we congratulate him for his well documented position supporting that cardiac denervation does play a role in exercise limitation after heart transplantation. In addition to nicely describing the cardiovascular adjustments during exercise, Dr. Andreassen also brought to the forefront of this debate that cardiac denervation should not be viewed only through its repercussion on heart rate but also through its effects on cardiac inotropy.

Nevertheless, HTx patients generally present with a normal systolic cardiac function that still improves during exercise, and this argument should be considered as secondary. Indeed, administration of Dobutamine failed to enhance peak aerobic capacity despite an immediate rise in cardiac output during exercise (8).

Similarly, although the heart rate response to exercise has been shown to be related with exercise capacity (1), improving the heart rate reserve by exercise training or L-arginine supplementation failed to improve patients’ exercise capacity (2, 4). Accordingly, a controlled trial of exercise rehabilitation after heart transplantation demonstrated that exercise capacity improvement occurred only in the training group, whereas exercise-induced heart rate increase was similar in both the exercising and the control groups (7). This should apply to Htx, since, even in case of documented sinus node denervation, their resting heart rate can be decreased by endogenous sympathoinhibitory factors (5), thus likely allowing an increased heart rate span during exercise. Taken together, these data strongly support that peripheral limitations are major compared with central limitations when considering exercise capacity after heart transplantation.

Of course, other organ transplanted patients, including renal transplant recipients, might demonstrate muscular limitations (9), mainly related to physical deconditioning, immunosuppressive therapy, and/or to endothelial dysfunction. Such muscular impairments better explain the reduced peak heart rate during exercise. Indeed, it is well known that cardiac output does adapt to the metabolic demand (i.e., muscular demand) rather than the opposite. The main driving mechanism of the cardiac response to exercise relies on peripheral metabolic need (3), which is likely to be reduced in Htx. A potential cardiac limitation can thus only be unmasked when Htx patients perform exercise of very high intensity or duration.

In conclusion, peripheral factors do generally play a major role in exercise limitation after heart transplantation, with an exception that confirms the rule: “For gold, heart rate matters” (10).

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