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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˙O2 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
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 DRS. RICHARD, ZOLL, METTAUER, 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).

REFERENCES