The following letters are in response to the Point:Counterpoint: Cardiac denervation does/not play a major role in exercise limitation after heart transplantation.

To the Editor: Denervation affects greatly cardiac function in HTx recipients. However, it is not the main determinant of their reduced aerobic performance (1, 6). Indeed, the latter depends on complex interactions among cardiac, pulmonary, neurohormonal, vascular, and skeletal muscle function (or “dysfunction”). The relative role of each of these factors may vary depending on donor’s heart characteristics, recipient clinical history, and time after HTx (4). In typical adult HTx recipients, increasing cardiac output (e.g., by priming exercise) does not enhance the kinetics of the metabolic phase of the \( \dot{V}O_2 \) on response to constant-load exercise (3). In addition, near peak muscle blood flow and its time constant at the onset of exercise are within normal values (2). A convincing evidence of the role of peripheral factors in limiting exercise performance after HTx derives from experiments in pediatric patients (5). Seven of fourteen young HTx recipients (“responders”) recovered normal peak heart rate (HR) values (maximum 203, average 177 ± 16 beats/min) and normal HR response kinetics on submaximal constant-load exercise, as if functional heart reinnervation had occurred. Despite the likely recovery of normal oxygen delivery to exercising muscles, peak oxygen consumption, and the time constant of the \( \dot{V}O_2 \) on response to the same submaximal workload were like those found in the seven HTX recipients (“nonresponders”) with persisting markers of heart denervation, i.e., reduced and slower, respectively, compared with healthy subjects. These findings are indicative of a metabolic impairment and strengthen the importance of muscle dysfunction rather than cardiac denervation in limiting aerobic exercise after HTx.

REFERENCES
1. Andreassen A. Point: Cardiac denervation does play a major role in exercise limitation after heart transplantation. J Appl Physiol; doi:10.1152/japplphysiol.00694.2007.

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To the Editor: Application of the Fick equation helps to elucidate the likely impact of a smaller increase of heart rate (1, 3) on the response to maximal exercise after cardiac transplantation and resulting denervation. In a control group of healthy 80-kg men aged 45 yr, with a resting oxygen consumption of 280 ml/min and an arteriovenous oxygen difference of 40 ml/l, the resting cardiac output would be 7 l/min (heart rate 78 beats/min, stroke volume 90 ml). In peak exercise, oxygen transport rises 10-fold (2), to 2,800 ml/min, with increases of oxygen extraction (3.5-fold), heart rate (2.21-fold to 172 beats/min), and stroke volume (1.29-fold to 116 ml).

Comparable figures for patients who had participated in 16 mo of endurance training after orthotopic cardiac transplantation (2) were body mass 76 kg, resting oxygen consumption 266 ml/min, and (assuming a similar peripheral oxygen extraction) a resting cardiac output of 6.65 l/min (heart rate 97 beats/min, stroke volume 68.6 ml). The peak oxygen intake had increased 26% over the postoperative value with training, to 2,128 ml/min, 8.0 times the resting value, with a heart rate of 148 beats/min (1.53 times rest), and a stroke volume of 103 ml (1.5 times resting). But if the heart rate had risen as in control subjects, the peak oxygen intake, at 3,020 ml/min would have exceeded the control value.

Plainly, the deficit of peak oxygen transport seen after cardiac transplantation would not occur if the heart rate rose as in healthy subjects.

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1. Andreassen A. Point: Cardiac denervation does play a major role in exercise limitation after heart transplantation. J Appl Physiol; doi:10.1152/japplphysiol.00694.2007.

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in patients with transplanted hearts. Thus in exercise involving a smaller fraction of total skeletal muscle mass, defects in extraction of oxygen in exercising muscle are indeed a major factor limiting exercise capacity.

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1. Andreassen AK. Point: Cardiac denervation does play a major role in exercise limitation after heart transplantation. J Appl Physiol; doi:10.1152/japplphysiol.00694.2007.

To the Editor: Evidence in favor of the concept that after heart transplantation (HT) both a reduced capacity of O2 delivery and a reduced capacity of O2 utilization are responsible for the reduced VO2 peak derives from a recent study by our group (4) in which we determined pulmonary VO2 and vastus lateralis muscle oxygenation indexes [by near infrared spectroscopy (NIRS)] during incremental exercise to exhaustion in 20 HT recipients (HTR), tested 33.9 ± 13.1 mo after surgery. As for NIRS, we considered an index (concentration changes of deoxygenated hemoglobin and myoglobin) that reflects fractional O2 extraction, that is the ratio between O2 utilization and O2 delivery in the tissue (2, 3). VO2 peak was lower in HTR vs. controls, whereas the VO2 vs. workload relationships were the same in the two groups. At submaximal loads, for the same VO2, we observed a higher O2 extraction in HTR vs. controls, suggesting an impaired capacity of O2 delivery in the patients. On the other hand, at exhaustion, the peak capacity of O2 extraction was lower in HTR vs. controls. Can the impaired capacity of O2 delivery, which we observed also at submaximal loads, be attributed solely to the impaired cardiac function (1)? Presumably not. Some peripheral vascular factors, such as endothelial dysfunction (5), are likely involved as well. In any case, our data suggest that both an impaired (central and peripheral) O2 delivery by the cardiovascular system and an impaired capacity of O2 utilization by skeletal muscles contribute to the persistently reduced exercise tolerance after HT. Objective tools to determine the relative contribution of the various impairments would be needed.

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1. Andreassen A. Point: Cardiac denervation does play a major role in exercise limitation after heart transplantation. J Appl Physiol; doi:10.1152/japplphysiol.00694.2007.
To the Editor: For patients with end stage heart failure, cardiac transplantation remains the most effective long-term therapeutic approach. Independent of the short- and long-term complications that accompany organ transplantation, the symptomatic benefit resulting from transplantation varies substantially. A variety of studies have examined the factors that predict exercise tolerance late after transplant. Among the clinical variables of relevance, the waiting time for transplantation and duration of postoperative intensive care treatment, likely due to long-lasting deleterious effects on skeletal musculature and the related microcirculation. In conjunction, peak exercise heart rate has also been shown to be a key determinant of peak oxygen consumption ($\dot{V}O_2$) and exercise test duration post transplant (2, 4, 5).

Given the key role of heart rate in determining the physiological response to exercise, we previously studied in detail the sympathetic control of the transplanted heart (3). We observed a progressive increase in the rate of release of norepinephrine (NE), the sympathetic neurotransmitter from the myocardium with increasing time post transplant. Moreover, this was even more apparent during exertion in which cardiac NE spillover was significantly lower early (<18 mo) after cardiac transplantation compared with control subjects (163 ± 50 vs. 1,876 ± 418 pmol/min, $P < 0.01$), whereas late postcardiac transplant subjects showed an intermediate response (1,080 ± 254 pmol/min). In parallel with these findings, the heart rate response in early post transplant was substantially flatter than that late post transplant. As such, while a multitude of factors contribute to the functional outcome after transplant, sympathetic reinnervation of the transplanted heart is a relevant and important process (1, 6).

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