Excessive Ventilatory Response to Exercise Persists Following Cardiac Transplantation

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Patients with heart failure (HF) frequently exhibit an excessive ventilatory response to exercise which is acutely unaltered by increasing cardiac output or decreasing pulmonary pressures. This excessive ventilation may result from respiratory muscle ischemia and fatigue. To investigate whether these ventilatory abnormalities resolve following cardiac transplantation (Tx), 10 patients with heart failure underwent exercise testing with respiratory gas analysis before and 1 year post transplant. Ventilatory response was also measured in 6 control subjects. Resting left ventricular ejection fraction (EF) and hemodynamic measurements were obtained. Post Tx, EF increased from 17±5 to 57±10%, pulmonary capillary wedge pressure decreased from 26±7 to 12±5 mm Hg, pulmonary vascular resistance decreased from 3.3±1.5 to 1.7±0.7 Wood Units, and cardiac index increased from 1.8±0.5 to 2.6 L/min/m^2 (all $p<0.05$). Minute ventilation (V_E) and respiratory rate were significantly reduced post Tx and comparable to normal values at submaximal workloads. Ventilatory responses at peak exercise and ventilatory equivalent for VCO_2 derived by linear regression analysis were as follows:

	VO_2 (ml/kg/min)	V_E (L/min)	V_E/VCO_2
Control	33±7.0	83±14	31±3
Pre Tx	11.5±1.6*	38±7*	52±10*
Post Tx	19.7±3.2*†	58±15*†	38±3*†

*$p<0.05$ Tx vs Control; †$p<0.05$ Pre vs Post Tx

Ventilatory response to exercise is significantly improved following cardiac transplantation. However, ventilation remains excessive. This may reflect an attenuated cardiac output response to exercise and/or abnormal intrapulmonary pressures.

BLOOD LACTATE LEVELS DO NOT CLOSELY REFLECT SKELETAL MUSCLE LACTATE METABOLISM IN CONGESTIVE HEART FAILURE

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Radioisotope tracer studies are helpful to determine the utility of blood lactate levels as a marker for anaerobic metabolism in CHF. Accordingly, arterial (a) and femoral venous (v) plasma lactate (La) concentrations and specific activity, and femoral arterial flow were determined during a constant infusion of C^{14}-lactate at rest (R) and during submaximal treadmill exercise (Ex, 63% of peak VO_2 for 30 min) in 6 patients with mild CHF (peak VO_2 19.1 ml/kg/min). Systemic lactate turnover (Rd) and lower extremity (LE) La uptake (Up) and release (Rel) were determined at isotopic steady state using Steele's equation, and compared to previous reports of normal (N) subjects. Results are as follows:

	[La] a (mM)	[La] v (mM)	Rd (µmol/kg/min)	LE La Up (µmol/min)	LE La Rel (µmol/min)
R-CHF	1.2	1.3	24.3	65	86
Ex-CHF	1.4	1.3	45.0	205	175
R-N	0.7	-	14.3	-	-
Ex-N	1.1	-	39.9	-	-

Even at rest, despite narrow arterial-venous La difference, Rd in patients with CHF appears to be greater than in N subjects, and there is substantial skeletal muscle Up and Rel of La. During Ex, arterial and venous La remain nearly constant despite 85%, 215% and 103% increases in Rd, LE La Up and Rel, respectively. Blood [La] appears to be an insensitive marker of La metabolism in CHF.

Skeletal Muscle Atrophy Contributes to Exercise Intolerance in Heart Failure

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Skeletal muscle mass is a determinant of exercise capacity in normal subjects. Therefore, a reduction in muscle mass could contribute to exercise intolerance in patients with heart failure. To evaluate skeletal muscle mass in heart failure, we measured percent ideal body weight (%IBW), 24-hr urine creatinine (Cr), serum albumen, pre-albumen, transferrin, and anthropometrics in 62 ambulatory patients with NYHA Class I-IV heart failure (EF 23±12%, peak VO_2 13±4 ml/kg/min). In 15 patients with heart failure and 10 age-matched control subjects, magnetic resonance imaging of the calf was performed. Muscle volume was calculated from the sum of the integrated area of muscle in 1 cm thick contiguous axial images from the patella to the calcaneus. A reduced skeletal muscle mass was noted in 68% of patients, as evidence by a decrease in Cr/height ratio <7.4 mg/cm and/or upper arm muscle circumference <5% of normal. Skeletal muscle mass averaged 13.2±3.8 kg and mid-arm muscle are 57.4±16.0 cm^2. Calf muscle volume was also reduced in patients with heart failure (N: 1274±311; HF: 1007±232 cm^3; $p<0.05$). Fat stores were largely preserved; triceps skinfold <5% of normal and/or IBW <80% occurred in only 8% of patients. Protein synthetic function was reduced in only 8% of patients. Significant positive linear correlations were observed between peak VO_2 and mid-arm circumference, muscle circumference, muscle area, skeletal muscle mass, and creatinine height index (all $p<0.05$). These observations demonstrate significant muscle atrophy in patients with heart failure. Furthermore, these findings suggest that loss of muscle mass contributes to exertional intolerance. Therapeutic interventions which increase muscle mass, such as the administration of growth hormone, may ameliorate exertional fatigue in these patients.

OBJECTIVE DETECTION OF MUSCLE FATIGUE IN PATIENTS WITH HEART FAILURE

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The ability of therapeutic interventions to improve exertional fatigue in heart failure has been difficult to document because no objective index of fatigue is available. In normal subjects, muscle fatigue during constant workload exercise is associated with an increase in electrical activity generated per contraction, due to recruitment of additional muscle fibers to compensate for fiber fatigue. To determine if this approach can be used to detect muscle fatigue in patients with heart failure, we monitored vastus lateralis surface electromyograms in 8 patients during maximal bicycle exercise (20 watt increments every 2 mins). The electromyogram was stored on tape and subsequently analyzed for root-mean-square voltage/contraction (RMSV). At each workload, the average RMSV noted during the first versus the last 30 seconds of the workload was compared. At workloads <50% of the maximal workload, the RMSV decreased by -17±20%. At the 2 highest workloads, patients reported muscle fatigue and exhibited marked increases in RMSV (+46±24%). These data indicate that the surface electromyogram can be used to detect muscle fatigue in patients with heart failure. This technique may be useful in the evaluation of drugs designed to improve exertional fatigue in heart failure.