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Title: Effects of sildenafil intake on the dynamics of skeletal muscle oxygenation at the onset of and recovery from exercise in CHF

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Body: Rationale: Nitric oxide (NO) exerts an important role in temporally and spatially match microvascular O_2 delivery ($Q´O_{2mv}$) to utilization in the skeletal muscle. Objective: To investigate the effects of increased nitric oxide (NO) bioavailability induced by sildenafil intake on muscle $Q´O_{2mv}$–to-oxygen uptake ($V´O_2$) matching at the transition to and from exercise in patients with chronic heart failure (CHF). Methods: 10 males (ejection fraction= 27 ± 6 %) underwent a supra-gas exchange threshold exercise test to the limit of tolerance 1 hour after sildenafil (50 mg) or placebo intake. The dynamics of $V´O_2$, fractional O_2 extraction in the vastus lateralis (~ [deoxy-Hb+Mb] by near infrared spectroscopy), and cardiac output (CO) were evaluated by non-linear regression procedures. Results: Sildenafil increased exercise endurance compared to placebo by ~ 20 %, an effect that was related to faster on- and off-exercise $V´O_2$ kinetics ($p<0.05$). Active treatment, however, failed to accelerate CO dynamics ($p>0.05$). On-exercise [deoxy-Hb+Mb] kinetics were slowed by sildenafil with a subsequent response “overshoot” being significantly lessened or even abolished. In contrast, [deoxy-Hb+Mb] recovery was faster with sildenafil (~ 15 %). Improvements in muscle oxygenation with sildenafil were closely related to faster on-exercise $V´O_2$ kinetics and greater increases in exercise capacity ($p<0.05$). Conclusions: Sildenafil intake enhanced on- and off-exercise $Q´O_{2mv}$-to- $V´O_2$ matching and $V´O_2$ kinetics with positive consequences on exercise tolerance in CHF. The lack of effect on CO suggests that improvement in blood flow to and within skeletal muscles underlies these effects.