Digoxin effects on muscle strength, fatigue and K^+ fluxes during exercise in healthy young adults

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The Na^+,K^+ATPase enzyme constrains muscle K^+ loss and Na^+ gain and is vital for skeletal muscle contractility, but our recent studies have found that maximal Na^+,K^+ATPase activity is depressed with fatigue. We investigated the effects of the specific Na^+,K^+ATPase inhibitor digoxin on muscle strength, fatiguability and performance; and on K^+ fluxes across active and inactive muscles during exercise.

Ten active, but not well-trained healthy volunteers (9 M, 1 F), with normal ECG, plasma electrolytes, renal function, and no history of adverse cardiovascular events gave written informed consent. A series of exercise tests were performed after taking digoxin (DIG, 0.25 $mg.d^{-1}$) or a placebo (CON) for 14 d, in a randomised, counterbalanced, cross-over, double blind design study, with trials separated by 4 weeks.

Quadriceps muscle strength (peak torque at 0-360°/s) and fatiguability during 50 maximal contractions (fractional decline in peak torque at 180°/s) were measured on day 13 on a Cybex isokinetic dynamometer. All subjects performed incremental cycle ergometer exercise to measure VO_{2peak} and to determine 33, 67 and 90% VO_{2peak} work rates. Subjects also performed an incremental test using concentric, dynamic finger flexor contractions to determine their peak work rate (WR_{peak}). On day 14 subjects completed two invasive trials separated by ~2 h. A finger flexion exercise trial comprised three 1-min bouts, then a final bout to fatigue, at 100% WR_{peak}. Two-legged cycling comprised 10 min each at 33% and 67% VO_{2peak}, then to fatigue at 90% VO_{2peak}. Radial arterial (a) and deep antecubital venous (v) blood was sampled simultaneously at rest, before and during each exercise bout and in recovery, for both exercise trials.

Serum digoxin was 0.7±0.2 nM at day 13 and 0.8±0.2 nM at day 14 (Mean±SD) in the DIG trial, and < 0.4 nM for CON. Muscle peak torque and the fatigue index (CON 0.57±0.10 *vs* DIG 0.54±0.09) were unchanged by digoxin. Time to fatigue during finger flexion exercise was not significantly affected by digoxin (CON 236±211 *vs* DIG 157±118 s, n=9). During finger flexion exercise, each of $[K^+]_a$, $[K^+]_v$ and $[K^+]_{a-v}$ were greater with exercise in CON (by 0.37±0.21, 1.29±0.84 and -0.89±0.69 mM), and similarly with DIG (by 0.34±0.36, 1.12±0.87 and -0.69±0.69 mM). The unchanged $[K^+]_{a-v}$ suggests unaltered K^+ release from contracting muscles with DIG. Time to fatigue during leg cycling exercise was not significantly affected by digoxin (CON 254±125 *vs* DIG 262±156 s). During leg exercise, each of $[K^+]_a$, $[K^+]_v$ and $[K^+]_{a-v}$ were greater with exercise than at rest in CON (by 2.51±0.83, 1.22±0.52 and 1.29±0.68 mM), but none were modified by DIG (by 2.62±0.57, 1.18±0.73 and 1.43±0.78 mM). The unchanged $[K^+]_{a-v}$ suggests unaltered K^+ uptake by inactive muscles with DIG.

In summary, DIG at therapeutic levels did not adversely affect muscle performance, $[K^+]$ or K^+ fluxes during exercise in healthy young adults. Whether this reflects inadequate digitalization, a safety tolerance to small reductions in functional Na^+,K^+ATPase, or limited adverse effects of digitalization when muscle Na^+,K^+ATPase is normal (i.e. high) is unclear.

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