Abnormal muscle Na^+,K^+-pumps, plasma K^+, and exercise limitation in renal failure patients

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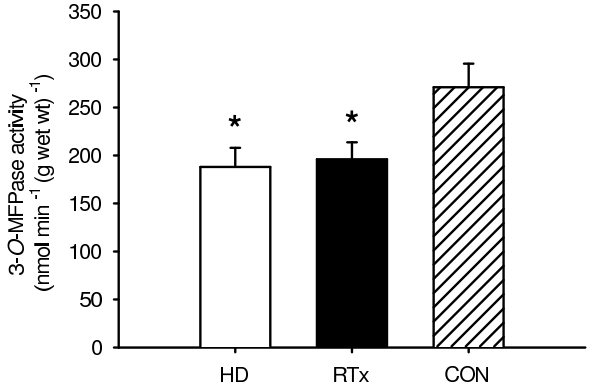
Patients with chronic kidney disease demonstrate an abnormally low exercise performance, which has been linked to impaired extrarenal K^+ regulation (Sangkabutra *et al.*, 2003). The cause of the impaired skeletal muscle K^+ regulation is unknown, but skeletal muscle Na^+,K^+-ATPase activity is subnormal in uraemic rats (Goecke *et al.*, 1991). In renal transplantation recipients (RTx), exercise performance is improved. Whether this is due to improved extrarenal K^+ regulation is unknown. Therefore, this study investigated whether plasma K^+ regulation during an incremental cycle test to fatigue was 1) impaired in haemodialysis patients (HD), 2) improved in RTx compared to HD, and 3) correlated to exercise performance. We also investigated whether skeletal muscle Na^+,K^+-ATPase activity and content were impaired in HD and RTx.

Ten HD, nine RTx, and ten age-, body mass-, height- and gender-matched controls (CON) performed incremental cycle exercise to fatigue, to measure peak oxygen consumption (VO_{2peak}) and arterial (HD, RTx) or arterialised-venous (RTx, CON) plasma [K^+] during exercise, corrected for plasma volume shifts. Leg-extensor isokinetic muscle strength was measured at 0, 60, 120, 180, 240, 300, and 360°.s^{-1} and fatiguability determined by the percentage decline in peak torque during 30 maximal contractions at 180°.s^{-1} and 0.5 Hz. Thigh muscle cross-sectional area (CSA) was measured by CT-scan. A resting biopsy was taken from the vastus lateralis muscle and analysed for Na^+,K^+-ATPase content (^{3}H-ouabain binding site content) and maximal activity (K^+-stimulated 3-*O*-methylfluorescein phosphatase activity). [Hb] was not different between the groups (HD 13.3±1.4 (mean ± SD), RTx 13.4±0.9, and CON 14.5±1.3 g dl^{-1}).

$VO_{2\ peak}$ was higher in CON than HD and RTx, by 35% and 32%, respectively (35.7±4.0, 26.4±6.0, 27.0±9.6 ml kg^{-1} min^{-1}, respectively, P<0.01). Leg-extensor muscle strength relative to CSA did not differ between groups, but was higher in CON when expressed relative to body mass (P<0.05). Leg-extensor fatiguability was lower in CON than in HD and RTx (13.3±5.9, 25.2±4.3, 23.8±10.7 %, respectively, P<0.01).



The rise in plasma [K^+] with exercise ($\Delta[K^+]$) only differed between groups at fatigue where CON was higher than HD and RTx (P<0.01). The $\Delta[K^+]$-to-work ratio was not different between groups (HD 14.9±8.5, RTx 20.8±15.6, CON 15.6±10.4 nmol L^{-1} J^{-1}, P=0.53) and was not correlated to $VO_{2\ peak}$ or leg-extensor fatiguability. Muscle ^{3}H-ouabain binding site content did not differ between HD, RTx, or CON (285 ± 77, 275 ± 46, 284 ± 56 pmol g wet wt^{-1}, respectively). The Figure shows higher maximal K^+-stimulated 3-*O*-MFPase activity in CON by 44% and 38%, compared to HD and RTx, respectively (P<0.05). For pooled data (n=28) 3-*O*-MFPase activity was correlated (P<0.05) with ^{3}H-ouabain binding site content (r = 0.42), VO_{2peak} (r = 0.45), maximum workrate (r = 0.43), total work done (r = 0.39), and $\Delta[K^+]$ during incremental exercise (r = 0.41), as well as kidney function measured by creatinine clearance (r = 0.44).

Whilst HD and RTx exhibited lower VO_{2peak} and higher leg-extensor fatiguability compared to CON, their $\Delta[K^+]$-to-work ratio during incremental exercise was not impaired. Muscle Na^+,K^+-ATPase content was normal in the patients, however muscle maximal Na^+,K^+-ATPase activity was reduced suggesting an abnormality in skeletal muscle Na^+,K^+-ATPase in renal failure patients. Furthermore, muscle maximal Na^+,K^+-ATPase activity was correlated to VO_{2peak}, suggesting a link with impaired incremental exercise performance in uraemia.

Goecke, I.A., Bonilla, S., Marusic, E.T. & Alvo, M. (1991) *Kidney International* **39,** 39-43.

Sangkabutra, T., Crankshaw, D.P., Schneider, C., Fraser, S.F., Sostaric, S., Mason, K., Burge, C.M., Skinner, S.L., McMahon, L.P. & McKenna, M.J. (2003) *Kidney International* **63,** 283-290.