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Free Communications 1: Exercise Physiology

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Chair: David Allen
Sudomotor responses during isometric exercise appear to be intensity- and muscle mass-dependent
C.J. Gordon, C.D. Haley, J.N. Caldwell and N.A.S. Taylor, Department of Biomedical Science, University of Wollongong, Wollongong, NSW 2522, Australia.

Cardiac frequency, mean arterial pressure and skin sympathetic nerve activity during isometric exercise, increase in proportion to exercise intensity (Vissing et al., 1991), while pressor responses also appear to be modulated by the size of the active muscle mass (Ray and Wilson, 2004). Sweating also responds to exercise intensity (Kondo et al., 2000), however, there is no information relating to the affect of muscle mass recruitment on sudomotor function. The hypothesis was tested that non-thermal sudomotor drive in the heat would be influenced by both exercise-intensity and the size of the recruited muscle mass.

Seven, resting (upright) males were heated (60 min) using a water-perfusion suit (37.2°C) and a climate-controlled chamber (36.7°C, 58% relative humidity) to induce steady-state sweating. Body temperature was clamped thereafter. Isometric handgrip and knee extension activations (60 s with 10 min rest) were performed at 30% and 50% maximal voluntary contraction (MVC) in a balanced order. Sweat rate ($m_{sw}$) was measured (1 Hz: 3.16 cm$^2$ capsules) at four sites (forehead, chest, and inactive forearm and thigh), and averaged. Cardiac frequency was monitored continuously (0.2 Hz), and mean arterial pressure was measured beat-by-beat.

Oesophageal and mean skin temperatures did not change during either rest or isometric exercise, verifying the veracity of the thermal clamp. Cardiac frequency displayed both an intensity- and a mass-dependence, resulting in the following pre- to post-activation changes (1 min): handgrip (5.9±1.4, 22.4±2.0 b.min$^{-1}$, 30 and 50% MVC; $P<0.05$); knee extension (14.5±1.4, 26.6±2.5 b.min$^{-1}$, 30 and 50% MVC; $P<0.05$). Similar to cardiac frequency, mean arterial pressure increased significantly during handgrip (10.1±1.9, 23.7±4.1 mmHg, 30 and 50% MVC; $P<0.05$), and knee extension (20.1±1.6, 32.1±2.8 mmHg, 30 and 50% MVC; $P<0.05$). Whilst pre-activation $m_{sw}$ baselines were similar, normalised increases in $m_{sw}$ from baseline, were intensity-dependent, but not mass-dependent: handgrip (0.093±0.027 and 0.212±0.035 mg.cm$^{-2}$.min$^{-1}$, 30 and 50% MVC; $P<0.05$; knee extension (0.140±0.017 and 0.198±0.026 mg.cm$^{-2}$.min$^{-1}$; $P>0.05$). However, the integrated sudomotor responses during isometric exercise appeared to reveal an intensity- and muscle mass-dependency: handgrip (3.15±0.70 mg.cm$^{-2}$ and 4.61±0.87 mg.cm$^{-2}$, 30 and 50% MVC); knee extension (4.17±0.48 and 5.53±0.89 mg.cm$^{-2}$). Whilst differences between handgrip and knee extension were non-significant (30% MVC $P=0.09$; 50% MVC $P=0.08$), post hoc analyses reveal our design to be under-powered; further testing is underway. In addition, following knee extension, $m_{sw}$ remained elevated compared to handgrip exercise. The possibility exists that the delayed $m_{sw}$ recovery, was mediated by intramuscular changes, which may be mass-dependent.

This study provides evidence that sudomotor responses to isometric exercise, during heat stress, may be exercise-intensity and muscle mass-dependent. If real, this latter observation is both novel and significant. Non-thermal factors have been suggested to modulate sweating during isometric exercise (Kondo et al., 2000). We now propose that motor unit recruitment may also influence sweating. In addition, the continued elevation of $m_{sw}$, but not body temperature, after isometric exercise, in particular knee extension exercise, may indicate that metaboreceptor stimulation, or an unidentified thermal factor, has augmented post-exercise sweating. This appears to also be mass-dependent.

Hydration indices in exertional heat stress
A.T. Garrett\textsuperscript{1,2}, N.G. Goossens\textsuperscript{1}, N.J. Rehrer\textsuperscript{1}, M.J. Patterson\textsuperscript{3} and J.D. Cotter\textsuperscript{1,}\textsuperscript{1} School of Physical Education, University of Otago, Dunedin, New Zealand, \textsuperscript{2}College of Education, University of Canterbury, Christchurch, New Zealand, and \textsuperscript{3}Defence Science and Technology Organisation, Melbourne, Australia.

Introduction. Hydration is a multi-factorial and dynamic phenomenon relating to the volume and composition of bodily fluid compartments. Nonetheless hypohydratation (lower than normal body water content) can be associated with reduced cognition and endurance exercise performance especially in the heat, and possibly with increased propensity or severity of heat illnesses. In regard to heat illness and performance, functionally relevant measures of hydration may be most validly measured during or immediately after the dehydrating stress. The reduction in body mass (%) is a traditional index of hydration, but plasma volume (PV) and plasma osmolality (Osmo\textsubscript{p}) might be viewed as having a more functional role in maintaining homeostasis under prolonged exertional heat stress.

Purpose. To examine the relationship between indices of hydration during dehydrating exercise in the heat, with variable rehydration.

Methods. Eighteen males (mean ±SD age 25 ±6 y, mass 74.9 ±4.4 kg, cycling peak oxygen uptake 4.7 ±0.3 L min\textsuperscript{-1}) undertook two to six 90-min heat exposures involving intermittent exercise in hot humid conditions (39.5°C, 60% r.h.) or continuous exercise in warm, moderately-humid conditions (35°C, 60% r.h.), with rehydration varying from none to full water replacement orally. Hydration-related indices measured before during and after exposures included plasma indices (AVP, Aldosterone, Na\textsuperscript{+}, Osmolality, ∆PV), thirst, urine (specific gravity (SG\textsubscript{U}), colour, osmolality), and body mass.

Results. Baseline reliabilities (mean difference) were variable between measures; AVP\textsubscript{p} 2.2%, Aldosterone\textsubscript{p} 25.8%, Na\textsuperscript{+} 0.3%, Osmo\textsubscript{p} 1.5%, thirst 15.9% and SG\textsubscript{U} 0.1%. Linear relations between hydration-related indices are shown in the table.

<table>
<thead>
<tr>
<th>Measure 1 (min - max)</th>
<th>Measure 2 (min - max)</th>
<th>$r^2$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>∆ body mass (-2.8 - 0.9%)</td>
<td>∆PV (-20.7 - 1.0%)</td>
<td>14%</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Osmo\textsubscript{p} (275 - 319 mosmol kg\textsuperscript{-1})</td>
<td>4%</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>AVP\textsubscript{p} (1 - 26 pg mL\textsuperscript{-1})</td>
<td>15%</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Aldosterone\textsubscript{p} (20 - 993 pg mL\textsuperscript{-1})</td>
<td>94%</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>Na\textsuperscript{+} (136 - 149 mmol L\textsuperscript{-1})</td>
<td>69%</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>Protein\textsubscript{p} (61 : 113 mg mL\textsuperscript{-1})</td>
<td>16%</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>SG\textsubscript{U} (1.000 - 1.030 units)</td>
<td>3%</td>
<td>0.24</td>
</tr>
<tr>
<td>Thirst (4 - 9 units)</td>
<td>%∆ body mass</td>
<td>81%</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>PV</td>
<td>13%</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>Osmo\textsubscript{p}</td>
<td>7%</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td>Na\textsuperscript{+}</td>
<td>6%</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>Protein\textsubscript{p}</td>
<td>46%</td>
<td>0.00</td>
</tr>
<tr>
<td>∆PV</td>
<td>Osmo\textsubscript{p}</td>
<td>14%</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Conclusion. Statistically-significant associations were evident between most pairs of hydration-related measures under conditions of dynamic exercise and ambient heat stress with varied rehydration. However, most associations were weak, and plasma osmolality, which is considered the most criterion measure, showed little association with other functional measures or with fieldable measures. The close relation between thirst and change in body mass has functional value but, oddly, was not reflective of a similarly close relation for factors that stimulate thirst.

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Plasma ammonia responses during heavy-intensity constant-load cycling in young and older individuals
S. Sabapathy, D.A. Schneider and N.R. Morris, School of Physiotherapy and Exercise Science, and Heart Foundation Research Centre, Gold Coast campus, Griffith University, Southport, QLD 4215, Australia.

A delayed and slowly increasing component of O$_2$ uptake kinetics may be observed when performing high intensity constant-load exercise (Barstow, 1994). Additionally, the increase in plasma ammonia concentration ([NH$_3$]) during high intensity cycling has been associated with the recruitment of type II fibres (Dudley et al., 1983). This study sought to examine the relationship between the slow component of O$_2$ uptake kinetics and plasma [NH$_3$] during constant-load cycling in healthy young and older individuals.

Seven young (mean age ± SD: 21.4 ± 2.8 yr) and 8 older healthy male adults (71.7 ± 2.7 yr) performed 7 min of heavy constant-load exercise. The power output for the constant-load tests was quantified as 50% of the difference between the power output attained at the gas exchange threshold and that achieved at peak O$_2$ uptake. The kinetics of O$_2$ uptake measured during constant-load exercise (including the slow component amplitude) were characterised using established non-linear regression modelling techniques (Sabapathy et al., 2004), as illustrated in the Figure. Plasma [NH$_3$] was measured at rest, following 3 min of unloaded cycling, and at 3 and 7 min of constant-load exercise.

The amplitude of the slow component was 406 ± 65 mL/min in the young and 217 ± 59 mL/min in the older subjects. Plasma [NH$_3$] values measured after 3 min of unloaded cycling and at 3 min of constant-load exercise were not significantly different from resting values, but increased significantly ($P<0.01$) between 3 and 7 min of exercise in both groups and correlated significantly ($P<0.05$) with the slow component (Young: $r = 0.79$; Older: $r = 0.75$).

While these findings do not indicate a causal link between the two variables, they could be related to a common physiological mechanism. The increase in [NH$_3$] observed is consistent with a progressive recruitment of type II muscle fibres during the slow component phase of exercise in both young and older individuals. The measurement of plasma [NH$_3$] during high-intensity exercise could provide a relatively non-invasive index of muscle fiber recruitment patterns.

Abnormal muscle Na\(^{+}\),K\(^{+}\)-pumps, plasma K\(^{+}\), and exercise limitation in renal failure patients
A.C. Petersen\(^1\), M.J. Leikis\(^2\), K.T. Murphy\(^1\), J.A. Leppik\(^1\), X. Gong\(^1\), A.B. Kent\(^2\), L.P. McMahon\(^2\) and M.J. McKenna\(^1\), \(^1\)Muscle, Ions and Exercise Group, Centre for Ageing, Rehabilitation, Exercise and Sport, School of Human Movement, Recreation and Performance, Victoria University, Melbourne, VIC 8001, Australia and \(^2\)Department of Nephrology, Royal Melbourne Hospital, Department of Medicine, University of Melbourne, Melbourne, VIC 3052, Australia.

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\(_{2}\)\(_{\text{peak}}\)) and arterial (HD, RTx) or arterioled-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 fatigability 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\(_{2}\)\(_{\text{peak}}\) 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 fatigability 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\(_{2}\)\(_{\text{peak}}\) or leg-extensor fatigability. 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-MFase activity in CON by 44% and 38%, compared to HD and RTx, respectively (\(P<0.05\)). For pooled data (n=28) 3-O-MFase activity was correlated (\(P<0.05\)) with \(^3\)H-ouabain binding site content (\(r = 0.42\)), VO\(_{2}\)\(_{\text{peak}}\) (\(r = 0.45\)), 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\(_{2}\)\(_{\text{peak}}\) and higher leg-extensor fatigability 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\(_{2}\)\(_{\text{peak}}\), suggesting a link with impaired incremental exercise performance in uraemia.

The effect of eccentric exercise on plasma K$^+$ regulation and skeletal muscle Na$^+$.K$^+$-ATPase activity and content

J.A. Bennie$^1$, C.A. Goodman$^1$, M.J. Leikis$^2$ and M.J. McKenna$^1$, $^1$Muscle, Ions and Exercise Group, School of Human Movement, Recreation and Performance, Centre for Ageing, Rehabilitation, Exercise and Sport, Victoria University, PO Box 14428, Melbourne, VIC 8001, Australia and $^2$Department of Nephrology, Royal Melbourne Hospital, Department of Medicine, University of Melbourne, Melbourne, VIC, Australia.

Intense exercise results in considerable muscle K$^+$ efflux, with consequently increased muscle interstitial [K$^+$] and reduced intracellular [K$^+$]. These changes and the reduction in transcellular [K$^+$] gradient have been linked with impaired skeletal muscle excitability and contractility (Sejersted & Sjøgaard, 2000). Eccentric exercise causes damage to involved muscles, with a commonly observed consequence being a reduction in the structural integrity of the sarcolemma and T-tubular system and release of intracellular proteins (Allen et al., 2005). Hence, it is possible that the Na$^+$.K$^+$-ATPase inserted in these membranes may also be impaired, which may therefore also affect plasma [K$^+$] and Na$^+$ and K$^+$ regulation in skeletal muscle. There have been no published investigations into the effects of unaccustomed eccentric exercise on plasma [K$^+$] or on Na$^+$.K$^+$-ATPase activity and content and these were therefore investigated here. It was hypothesized that eccentric exercise would progressively increase plasma [K$^+$] and depress both the Na$^+$.K$^+$-ATPase activity and content immediately post-exercise.

Six healthy subjects (3 males, 3 females) performed a single bout of one-legged, eccentric, knee extensor exercise, comprising 300 repetitions of maximal eccentric contractions, at 30$^\circ$/s. The eccentric exercise bout was conducted on an isokinetic dynamometer, and consisted of 10 sets of 30 repetitions, with a 1 min recovery period separating each set. Maximal isometric knee extensor torque was assessed pre- and immediately post-exercise and at the end of sets 1, 2, 4, 6, 8, and 10. Muscle biopsies were taken from the vastus lateralis muscle at rest and immediately post-exercise and analysed for maximal Na$^+$.K$^+$-ATPase (3-O-MFPase) activity and Na$^+$.K$^+$-ATPase ($[^3]$H-ouabain binding) content.

Maximal isometric torque of the knee extensors was depressed (P <0.05) immediately post-exercise by 26 ± 11% (Mean ± SD). Total work performed by the knee extensors during each set remained constant from sets 1 to 5 after which it was reduced for all subsequent sets (P <0.05). Plasma [K$^+$] was elevated above rest by the end of the first set (P <0.05). However, despite the declining work output, plasma [K$^+$] remained elevated throughout the remainder of the exercise bout. The rise in [K$^+$] above rest (Δ[K$^+$]) expressed relative to the amount of work performed (ΔK$^+$/work ratio), increased from set 2 to set 4 (P <0.05) and then remained elevated through to set 10. Although tendencies for declines were noted, no significant change was found after eccentric exercise in maximal 3-O-MFPase activity (P = 0.095) or $[^3]$H-ouabain binding site content (P = 0.074).

In conclusion, the observation that plasma [K$^+$] remained elevated despite a decrease in work performed by the knee extensor muscles suggests an impairment in K$^+$ regulation during prolonged maximal eccentric exercise. This may reflect a reduction in muscle Na$^+$.K$^+$-ATPase and/or damage to the muscle membranes.

N-acetylcysteine infusion enhances skeletal muscle Na\textsuperscript{+},K\textsuperscript{+}-ATPase activity and plasma K\textsuperscript{+} regulation, and delays fatigue, during prolonged submaximal exercise in well-trained individuals

C.A. Goodman\textsuperscript{1}, I. Medved\textsuperscript{1}, M.J. Brown\textsuperscript{2}, A.R. Bjorksten\textsuperscript{3}, K.T Murphy\textsuperscript{1}, A.C Petersen\textsuperscript{1}, S. Sostaric\textsuperscript{1}, X. Gong\textsuperscript{1} and M.J. McKenna\textsuperscript{1}, \textsuperscript{1}Muscle, Ions & Exercise Group, Centre for Ageing, Rehabilitation, Exercise and Sport, School of Human Movement, Recreation and Performance, Victoria University, PO Box 14428, Melbourne, VIC 8001, Australia, \textsuperscript{2}Department of Anaesthesia, Austin Health, Heidelberg, VIC, Australia and \textsuperscript{3}Department of Anaesthesia and Pain Management, Royal Melbourne Hospital, Melbourne, VIC, Australia.

The production of reactive oxygen species (ROS) in skeletal muscle has been linked with muscle fatigue (for reviews see Reid, 2001). Recently, we showed that intravenous infusion of the antioxidant N-acetylcysteine (NAC) increased each of muscle NAC (total and reduced), cysteine and glutathione (reduced) and improved prolonged submaximal exercise performance in well-trained individuals (Medved et al., 2004). We have found depressed Na\textsuperscript{+},K\textsuperscript{+}-ATPase activity in skeletal muscle during exercise, which may contribute to disturbed muscle ionic homeostasis and fatigue (Leppik et al., 2004). This study investigated whether ROS may be involved in this process, by examining the effect of NAC infusion on skeletal muscle Na\textsuperscript{+},K\textsuperscript{+}-ATPase activity and potassium (K\textsuperscript{+}) regulation during prolonged submaximal endurance exercise, in well trained individuals.

Eight well-trained subjects participated in a double blind, randomised, crossover design study, receiving either an NAC or saline (CON) infusion into a superficial forearm vein (Medved et al., 2003). NAC was intravenously infused at 125 mg.kg\textsuperscript{-1}.hr\textsuperscript{-1} for 15 min, then 25 mg.kg\textsuperscript{-1}.hr\textsuperscript{-1} for 20 min prior to and throughout exercise, which was continued until fatigue. Subjects completed cycling exercise comprising 45 min at 70\% \textit{VO}\textsubscript{2peak}, then to fatigue at 90\% \textit{VO}\textsubscript{2peak}. Muscle biopsies were taken from the vastus lateralis before exercise, at 45 min and at fatigue and analysed for maximal \textit{in vitro} Na\textsuperscript{+},K\textsuperscript{+}-ATPase activity (maximal 3-\textit{O}-methyfluorescein phosphatase, 3-\textit{O}-MFPase). Blood was sampled at pre-infusion, immediately prior to exercise, during exercise at 15, 30, 45 min and at fatigue. Blood was analysed for plasma [K\textsuperscript{+}] as well as blood haemoglobin concentration ([Hb]) and hematocrit (Hct).

Time to fatigue at 90\% \textit{VO}\textsubscript{2peak} was reproducible in preliminary trials (CV 5.6\pm0.6\%) and with NAC was enhanced by 20.8\pm9.1\% (NAC 6.4\pm0.6 vs CON 5.3\pm0.7 min, P\textless0.05) (Medved et al., 2004). Maximal 3-\textit{O}-MFPase activity decreased by 21.6\pm2.8\% at 45 min and by 23.9\pm2.3\% at fatigue when compared to rest (P\textless0.05). NAC attenuated the percentage change in maximal 3-\textit{O}-MFPase activity at 45 min (P\textless0.05) compared to control but not at fatigue. However, the change in 3-\textit{O}-MFPase activity to work ratio was attenuated by NAC both at 45 min and at fatigue (P\textless0.005). The rise in plasma [K\textsuperscript{+}] and plasma \Delta[K\textsuperscript{+}]-to-work ratio during exercise were both attenuated by NAC (P\textless0.05). There was no significant correlation between time to fatigue and each of maximal 3-\textit{O}-MFPase, rise in plasma [K\textsuperscript{+}] and plasma \Delta[K\textsuperscript{+}]-to-work ratio.

In conclusion, our data show that NAC infusion in well-trained individuals attenuated the depression in muscle Na\textsuperscript{+},K\textsuperscript{+}-ATPase and enhanced K\textsuperscript{+} regulation, which may be important in delaying fatigue during prolonged submaximal exercise. This suggests that ROS play a role in skeletal muscle fatigue and specifically in Na\textsuperscript{+},K\textsuperscript{+}-ATPase regulation and K\textsuperscript{+} regulation during submaximal exercise.