Novel quantitative phenotypes of exercise training in mouse models

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De Bono, J. P., D. Adlam, D. J. Paterson, and K. M. Channon. Novel quantitative phenotypes of exercise training in mouse models. Am J Physiol Regul Integr Comp Physiol 290: R926–R934, 2006.—Regular physical exercise has beneficial effects in many human disease states, including cardiovascular diseases, cancer, and depression. Exercise training of genetically modified mouse models may provide insight into the molecular mechanisms that underlie the beneficial effects of exercise. Presently, there is relatively little understanding of the normal physiology of mouse exercise. In this paper, we describe a novel computerized voluntary wheel-running system capable of recording and analyzing individual wheel rotations. Using this system, we demonstrate that C57BL/6 mice run considerable distances during the night in short bouts and at a preferred speed: the cruising speed. We find that the vast majority of running occurs around this cruising speed, which is close to the maximum speed at which the animal can run but is significantly higher than the average speeds recorded by simple digital odometers. We describe how these parameters vary with exercise training and demonstrate marked sex differences in the patterns of voluntary exercise. The results of this study have important implications for the design and interpretation of both voluntary and forced exercise experiments in mouse models. The novel parameters described provide more physiological quantitative measures of voluntary exercise activity and training and will extend the physiological utility of exercise training as a phenotyping tool in genetic mouse models.

Voluntary exercise; computerized monitoring; circadian rhythm; physiological hypertrophy

Exercise is an important contributor to improved health. Regular physical exercise in humans reduces cardiovascular risk (26) and reduces mortality in cardiovascular disease states (8, 21, 27). Increased levels of exercise have also been reported to have beneficial effects on conditions as diverse as cancer (9, 22), osteoporosis (10), and depression (4). Genetically modified mouse models are increasingly used to investigate the molecular mechanisms underlying complex disease states. Identification of the molecular mechanisms that underlie the beneficial effects of exercise may provide insight into novel therapeutic targets for the prevention and treatment of cardiovascular and other diseases.

Experimental exercise models in mice use either voluntary or forced activity. Forced models, such as swimming or treadmill running, use aversive stimuli to induce exercise (2). These systems have the advantage that animals can be made to exercise at reproducible distances and speeds. However, the experimental conditions are often stressful and nonphysiological; the stimulus to exercise is unpleasant (such as the treadmill shock bar or fear of drowning), and the pattern of activity is far removed from normal mouse behavior. Furthermore, experiments are normally performed in daylight hours, contrary to the murine diurnal pattern of nocturnal activity. It is likely that these factors may have major confounding effects on both the physiological responses to exercise and the molecular mechanisms underlying these responses. The alternative to forced exercise is voluntary wheel running. It has been widely demonstrated that mice will run spontaneously if given access to a freely rotating wheel (1, 2, 18, 24, 28). Voluntary-running activity occurs in a nonstressed environment and without disruption of the normal murine diurnal rhythm. Use of a running wheel also allows assessment of the training response over time. However, it is technically more challenging to monitor voluntary wheel running during exercise and derive reliable measures of true exercise performance, which are necessary to quantify phenotypic differences between groups of mice with optimal biological and statistical power (6, 7).

Previous studies have relied on click counters or odometers to monitor total distance run (17, 20). Some have also gone on to estimate total time spent running and thus the average speed of animal groups (1, 13–15, 17, 18, 20, 28). However, these parameters are unable to provide a detailed analysis of exercise activity in relation to true running speeds, bouts of running, or diurnal pattern of exercise. Accordingly, we now describe the development of a novel computerized exercise monitoring system that provides a sophisticated analysis of voluntary wheel running in C57BL/6 mice. We find that mice run in short bursts at a single preferred running speed: the cruising speed. We quantify in detail how animals train to voluntary wheel running and demonstrate profound differences between male and female mice in exercise behavior patterns and in their physiological response to exercise training. A number of physiological measures have been previously described, including cardiac and skeletal muscle hypertrophy and changes in body weight (1, 15, 19). It has been suggested that there are gender differences in physiological cardiac hypertrophy and changes in body weight (13), although most studies only look at male mice (1, 19) and other studies have not confirmed this finding (25). We present further evidence confirming the gender differences in cardiac hypertrophy and also showing significant differences in body weight change in response to exercise.

Methods

Animals. All animals were 10- to 11-wk-old C57BL/6 (15) strain littermates from an inbred colony. Mice were provided with standard chow and water ad libitum and housed singly at 24°C in individually ventilated cages (IVC, Techniplast Italy). All mice were exposed to a 12-h light-dark cycle.
Voluntary exercise. Mice were randomly assigned to either exercise or sedentary groups. Exercise animals were provided with an angled rotating running track (Lillico, Surry, UK), circumference 37.8 cm, mounted on a greased steel axle (Fig. 1). Sedentary animals were provided with an identical nonrotating track. The angled running track was used in preference to traditional vertical wheels to allow the use of larger diameter wheels within IVC cages. Wheel running was monitored using a magnetic reed switch attached either to a digital odometer (Enduro 2, Cateye) or to a novel computerized exercise-monitoring system. This system consisted of the Micro 1401 (CED, Cambridge, UK), capable of simultaneously monitoring the individual rotations of the wheel from up to 44 animals, with wheel rotations recorded and analyzed by computer with Spike 2 software (CED).

Running parameters. The following running parameters were derived from the baseline activity data for each 24-h period. 1) Distance traveled represents the total number of wheel rotations \( \times \) wheel circumference. 2) Time represents time spent continuously exercising with a maximum interval between detected wheel rotations of 5 s. 3) Average speed represents the total distance run/total running time during each 24-h period. 4) Maximum speed represents the speed at the upper 99th percentile of wheel rotation speeds from all individual wheel rotation time intervals in a 24-h period. 5) Cruising speed represents the modal running speed in the distribution of running speeds from all individual wheel-rotation time intervals in a 24-h period. 6) Interquartile range (IQR) represents the time difference between the 25th and 75th percentile of the time intervals of individual wheel rotations in a single 24-h period. 7) Mean day-to-day variation in time spent running was calculated as the mean of the differences in time spent running on by an individual animal on consecutive days as a percentage for the total time spent running on those days. 8) Trained: for the purposes of this study, a trained animal was defined as a subject in which all the parameters of exercise listed above had reached a plateau.

Physiological response to exercise. After 5 wk, animals were euthanized by cervical dislocation under terminal anesthesia with isoflurane. This time point was selected because preliminary experiments showed that all running parameters had achieved a plateau for at least 10 days. Animal weights and body length (measured form the tip of the nose to the base of the tail) were determined; the heart and ankle flexor muscles (soleus and gastrocnemius after removal of plantaris) were dissected from each animal, and wet weights were determined. The tibia was then disarticulated and measured.

Statistics. Results are expressed as means \( \pm \) SE. Serial data for the running parameters measured were compared in male and female mice using an ANOVA for repeated measures. Where appropriate, different time periods were analyzed separately. Animal and organ weights were analyzed with a nonpaired \( t \)-test. Heart weights were also analyzed using an ANCOVA with either body weight as a single covariate or with total running distance, body weight, and sex as covariables.

RESULTS

Assessment of exercise performance using simple odometers. Animals ran freely on the angled running track, adopting a stationary running posture on the lower horizontal surface of the running track (Fig. 1). Mouse running performance was first monitored using digital odometers activated by wheel rotation (Enduro 2). This allowed measurement of total distance run, time spent running, and thus calculation of average speed. When supplied with a freely rotating wheel, C57BL/6 mice spontaneously ran large distances, with female mice running farther than males at all time points (Fig. 2A; \( P < 0.001 \) for \( \text{days} 1–35 \)). The daily total distance run increased as the animals trained, reaching a peak at day 12 in female mice and day 16 in male animals. The total distance run was dependent on both the time spent running and the average speed of the animal.

The total time spent running increased rapidly in the first few days of training in female mice, reaching a plateau by \( \text{days} 5–6 \) (Fig. 2B). In male mice, the time spent running increased more slowly and did not reach a plateau until \( \text{days} 14–16 \). Female animals spent considerably longer time running than male mice (\( P < 0.001 \) for \( \text{days} 1–35 \)).

Variability in voluntary exercise. Both the total distance covered and the time spent running varied considerably from day to day for individual animals (Fig. 2, C and D). This variability was much greater in female mice than in males. Mean day-to-day variation in time spent running normalized
for total time was 25.0 ± 2.1% in females and 17.1 ± 1.5% in males (P < 0.01).

Average speed. In contrast to both the distance run and time spent running, the average running speed of a mouse was much less variable from day to day and increased logarithmically during training (Fig. 3). Initially, female mice had a higher average running speed (P < 0.001 for days 1–15). By week 3, the average speed of male mice had reached the same level as females, and in trained animals there was no significant gender difference (P = 0.144 for days 16–35). The persisting gender difference in distance run in trained animals was therefore largely due to the increased time spent running in female mice (Figs. 2, A and B, and 3A).

Advanced exercise analysis using a novel computerized system. To further analyze the nature and timing of voluntary wheel running, we developed a computerized exercise-monitoring system that allowed detection and analysis of both the speed and time of all individual wheel rotations within a 24-h period (Fig. 4A). This system could calculate the same parameters measured by the digital odometers with an extremely close degree of correlation (coefficients of variation: time 2.75%, distance 1.60%, average speed 1.31%) (3). Furthermore, the computerized monitoring allowed each individual wheel rotation to be accurately detected and timed (Fig. 4A). An interval histogram of the time taken for each wheel rotation showed a highly skewed distribution (Fig. 4B). Novel parameters of mouse wheel running were derived from the interval histogram of all wheel rotation intervals from a 24-h period.

Cruising speed. The vast majority of mouse wheel running occurred around a single speed that we defined as the cruising speed (Fig. 4, A and B). This modal speed was much higher than the average speed (Figs. 3A, 4A, and 7B). Mice spent very little time running at their calculated average speed. In fully trained mice, 75 ± 0.96% of wheel rotations occurred at a speed faster than the average speed.

Maximum speed. The true maximum speed of mouse wheel running was calculated from the upper 99.9th percentile of the interval histogram. In trained animals, there was only a small difference between the cruising speed of running and the maximum speed that the animals could achieve (cruising speed 87 ± 0.95% of maximum speed).

Diurnal pattern of exercise. The computerized system recorded the precise times of mouse wheel-running activity, allowing analysis of both the overall circadian pattern of exercise and the duration and average speed of individual exercise bouts. Mice ran almost exclusively during the night (Fig. 5) in multiple short bouts (Fig. 6, A and B). The median interval between bouts was similar in males and females and remained consistent throughout training (males 30.4 ± 3.0 s, females 30.2 ± 3.2 s). Female mice ran throughout the night,
after the first week, there was no significant gender difference in IQR \((P = 0.4\) for \textit{days} \(8–35\)). Both the cruising speed and maximum speed increased more slowly and over a longer time course than the average speed or IQR, reaching a peak at \(\sim 17\) days in females and \(22\) days in males (Figs. \(3A, 4C,\) and \(7, C\) and \(D\)). During the initial period of training, female mice had a higher cruising speed and maximum speed than males \((P < 0.001\) for cruising speed, \(P < 0.05\) for maximum speed for \textit{days} \(1–21\)), but there were no significant gender differences in these parameters after training \((P = 0.11\) for cruising speed, \(P = 0.674\) for maximum speed for \textit{days} \(22–35\)).

**Physiological response to exercise training.** After 5 \textit{wk} of voluntary exercise, male mice had a significantly lower body weights than their sedentary littermates \((P = 0.001\)\) (Table 1). In contrast, there was no difference in body weight between sedentary and exercised female mice \((P = 0.54\)\). There was significant cardiac hypertrophy in exercised female mice. Both absolute heart weight and heart weight adjusted for body weight \((P < 0.001\)\), tibia length \((P = 0.01\)\), and body length \((P < 0.001\)\) were significantly increased. In contrast, male mice had a small increase in absolute heart weight, which was not statistically significant when analyzed with an unpaired \(t\)-test \((P = 0.63)\) or when adjusting for tibia length \((P = 0.8)\) or body length \((P = 0.48)\) but was when adjusting for body weight \((P = 0.028)\). To determine whether this was entirely due to the fall in body weight in males, an ANCOVA was performed with body weight as a covariate, demonstrating a significant although small effect of exercise \((P < 0.015)\) on heart weight in male mice also. A multivariate analysis adding exercise distance as a covariate did not demonstrate a significant association between running distance and heart weight when body weight and sex were included in the model (although this study was not specifically powered to look at the effect of running parameters on physiological hypertrophy). There were no significant differences in the soleus and gastrocnemius muscle wet weights in response to exercise in either sex except when adjusted for body weight in male mice (Table 1).

**DISCUSSION**

In this paper, we described the development of a novel high-capacity computerized voluntary wheel-running system to precisely monitor exercise activity in mouse models. Using this system, we presented a detailed analysis of wheel running in C57BL/6 mice and described new physiological measures of exercise performance. First, we demonstrated that mice run in short bouts at a preferred running speed or “cruising speed,” close to their maximum speed. This is significantly higher than the average speed traditionally measured. Second, we confirmed and expanded previous observations of profound gender differences in running performance. Third, we demonstrated significant gender differences in body weight and cardiac hypertrophy in response to exercise. We used C57BL/6 strain mice because these are widely used in murine genetic studies and because C57BL/6 is the strain from which the published mouse genome was derived. The parameters described have the potential for improved characterization and quantification of exercise phenotypes in mouse models and have important implications for investigators who use both voluntary and forced exercise paradigms.

**Running profile.** The key feature that allowed for the detailed exercise phenotyping by the computerized system is the
detection and analysis of each and every individual wheel rotation during a 24-h period. Thus, in contrast to the wheel-activated digital magnetic counters used by many groups (1, 3, 13, 18, 28), it was possible to continuously monitor running speed. We used this system to demonstrate the existence of a single preferred running speed or “cruising speed.” This was extremely close to the maximum speed at which mice could run. There was no evidence that individual mice will spontaneously run at different speeds. Exercise training was associated with increased cruising speed, enhanced maximum speed, and a reduction in the IQR of running speeds. It is unlikely that cruising speed reflects an intrinsic property of the running wheel because there was significant variation between animals and an almost 100% increase during training. This may suggest that mouse physiology is adapted to a single level of exercise, close to the physiological maximum, in contrast to humans who show a graded response.

Monitoring of voluntary wheel running. Previous authors have used average speed as a marker of exercise performance (13, 15, 18, 28). Average speed is consistent in individual mice and increases over the period of voluntary exercise training in a logarithmic fashion. However, there are problems with the use of average speed as a marker of exercise performance and training. To calculate average speed, both distance and an estimate of the time spent running are needed. The latter requires an assumption to be made as to the longest gap
between wheel rotations consistent with continued slow running, as opposed to a cessation of running. Most commercially available digital magnetic counters start recording with the first wheel rotation and stop recording at a set time after the last wheel rotation (2 s for the Enduro-2 odometer). Any pauses longer than this reset the counter. The effect of this assumption is that, if animals run at a very slow pace, e.g., 30 wheel rotations/min (11.34 m/min or 0.68 km/h using a 2-s pause on the wheels described in this paper), then no running will be recorded. Alternatively, if a longer set period is used (e.g., 5 s), then the recorded time spent exercising will be significantly inflated. No such assumptions are needed to measure cruising speed and maximum speed, the novel parameters described in this manuscript.

It is clear that the vast majority of true wheel-running activity occurs at a speed considerably greater than the average speed, with over three-quarters of wheel rotations occurring faster than the average speed. This is because the average speed during a 24-h period is artificially reduced by the number of slower wheel rotations. There is no obvious pattern to these rotations, and they are likely to represent animals playing or coasting on the wheel rather than true wheel running (7, 14). Indeed, the rapid rise in average speed in the first couple of days of training and the corresponding decrease in the IQR may correspond to behavioral changes as the animals learn to run on the wheel, as opposed to true physiological training (1). Cruising speed and maximum speed rose more slowly, suggesting that these parameters may better reflect improved cardiorespiratory and muscular performance. Accordingly, the biological and statistical power of these parameters to detect differences may be superior to traditional measures, such as average speed. These parameters may also provide alternative measures for running trait-selection experiments by allowing identification of mice with high running speeds as an alternative selection strategy to using mice with longer running distances (24, 25).

**Implications for forced exercise experiments.** Many groups use forced treadmill testing to look for phenotypic differences between mice (2, 11, 13, 18, 19). Most use a ramped protocol, where the speed of treadmill rotation and/or the angle of slope incline is gradually increased and where the mice exercise continuously to the point of exhaustion (typically at least 30 min). The initial speed of the treadmill is often as low as 4 m/min (0.24 km/h) and ranges up to 42 m/min (2.52 km/h) (11). Forced treadmill running is also used to exercise train animals (5, 16, 19, 23). Again, the training protocols involve mice running for long periods of time at speeds very different from the cruising speeds described in this paper, typically 15 m/min (0.9 km/h) (5, 12). We have demonstrated that mice preferentially run in short bursts of ~150-s duration. This confirms previous data from a short-period video-recording study (7), which demonstrated that running occurs in short bouts and showed differences in running bouts between selected mouse lines. Animals in our experiments never ran for periods as long as those used in the treadmill experiments. In addition, mice have a single preferred running speed. These results suggest that mice are maladapted to the protocols presently used in treadmill-running experiments. Differences in exercise performance measured with a treadmill may therefore reflect physiological differences in ability to run at the

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Fig. 5. Circadian pattern of wheel running in trained male and female C57BL/6 mice. Distances run in each hour were averaged for 5 days (days 21–26 after the initiation of voluntary wheel running). Female animals ran farther in the second half of the dark period. *P < 0.01.

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Fig. 6. Analysis of running bouts in male and female C57BL/6 mice for 5 wk after initiation of voluntary wheel running (n = 11 females and 10 males). A: number of bouts in a 24-h period. B: mean duration of individual exercise bouts in a 24-h period.
experimentally chosen speed rather than a lack of general endurance. Furthermore, forced running at speeds and for durations far removed from the normal pattern of murine voluntary activity may exacerbate the stress response and potentially confound physiological or molecular data obtained from these animals.

The discrepancy between average speed and both cruising speed and maximum speed may partly explain the lack of correlation observed between markers of voluntary wheel-running performance and forced treadmill testing. Lerman et al. (18) reported that mean odometer average speed of voluntary wheel running was only 57% of maximum speed achieved.

Table 1. Physiological response to exercise

<table>
<thead>
<tr>
<th></th>
<th>Female Sedentary</th>
<th>Female Exercise</th>
<th>P</th>
<th>Male Sedentary</th>
<th>Male Exercise</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 15)</td>
<td>(n = 15)</td>
<td></td>
<td>(n = 13)</td>
<td>(n = 13)</td>
<td></td>
</tr>
<tr>
<td>Weight, g at death</td>
<td>22.72±0.38</td>
<td>22.40±0.33</td>
<td>0.54</td>
<td>28.75±0.40</td>
<td>26.74±0.37</td>
<td>0.001</td>
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<tr>
<td>Absolute heart weight, mg</td>
<td>106.9±3.43</td>
<td>123.4±3.31</td>
<td>0.001</td>
<td>130.8±3.33</td>
<td>133.0±2.90</td>
<td>0.63</td>
</tr>
<tr>
<td>Heart wt-to-body wt ratio, mg/g</td>
<td>4.70±0.11</td>
<td>5.50±0.11</td>
<td>&lt;0.001</td>
<td>4.55±0.078</td>
<td>4.98±0.10</td>
<td>0.028</td>
</tr>
<tr>
<td>Heart wt-to-tibia length ratio, mg/cm</td>
<td>56.4±2.4</td>
<td>66.1±2.6</td>
<td>0.01</td>
<td>69.0±2.2</td>
<td>68.2±2.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Heart wt-to-body length ratio, mg/cm</td>
<td>12.1±0.30</td>
<td>14.1±0.30</td>
<td>&lt;0.001</td>
<td>14.2±0.33</td>
<td>14.5±0.28</td>
<td>0.48</td>
</tr>
<tr>
<td>Ankle flexor wt-to-body wt ratio, mg/g</td>
<td>5.68±0.060</td>
<td>5.73±0.087</td>
<td>0.68</td>
<td>5.52±0.11</td>
<td>5.86±0.054</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Values are means ± SE. Body weight, heart weight, and ankle flexor weight (gastrocnemius and soleus) measurements were made at the time of harvest.
on a treadmill by the same mice. Our data suggest that a comparison with average speed greatly underestimates the actual running speeds of voluntary wheel-exercised mice. The average speed-to-maximum speed ratio calculated in our voluntary-exercised mice is actually rather similar to the ratio of voluntary average odometer speed to maximum treadmill speed described by Lerman et al. (17) (48% of at the start of training, rising to 71% in trained animals). Furthermore, the maximum speed that we have defined from voluntary running, which is similar to values from video analysis studies (7), also conforms quite closely with previously described treadmill speeds achieved at the point of mouse exhaustion (11, 19). Thus measures of time taken for mouse exhaustion using a ramped protocol, with increasing treadmill speed may be measures of the time taken for the treadmill to reach the animal’s maximum running speed rather than a true reflection of endurance exercise capacity (13, 18).

Effects of gender on exercise training. We have confirmed previous reports of significant differences in voluntary wheel-running activity between males and females (13, 24). Female C57BL/6 mice ran on average 40% further than male mice. Initially, females ran faster and for longer; however, in trained animals, there was no gender difference in cruising speed or maximum speed. The difference in running distance was entirely due to increased running in the second half of the night in females. There was significantly more day-to-day variation in time spent running in female animals. The reasons for this are not clear but may relate to underlying estrus cycle. Physiological response to exercise training. We also report gender differences in the physiological response to exercise. Mice exercised in males had a considerably lower body weight than age-matched sedentary littersmates. In contrast, exercise was not associated with a fall in body weight in females but caused much greater cardiac hypertrophy (15.4%) than was seen in males (1.7%). Similar results have previously been reported (13, 25). Kohnilas et al. (13) also showed significantly greater cardiac hypertrophy in female C57BL/6 mice (15.9%) than in males (5%). Swallow and Garland (25) showed a smaller increase in heart weight in both female (3.99%) and than in males (5%). The reasons for this are not clear but may relate to underlying estrus cycle.

Implications for future work. The results of these data suggest accurate phenotyping of voluntary wheel running in mice can be improved by detailed analysis of instantaneous running speeds. This would allow the single preferred running speed or cruising speed to be determined along with a more accurately defined measure of maximum speed. Continuous monitoring can also provide insight into the number and duration of running bouts. This approach is likely to refine the effectiveness of exercise monitoring as a physiological phenotyping tool for mouse models.

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