Cardiovascular effects of treadmill exercise in physiological and pathological preclinical settings

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EXERCISE REPRESENTS one of the most severe, yet physiological, stresses to the intact cardiovascular system and a crucial determinant of the use of metabolic substrates. Although treadmill exercise is characterized by a coordinated response of multiple organ systems, many of the important acute changes affect the cardiovascular system during physical training. Exercise studies are needed to obtain precious information about how the cardiovascular system responds under maximally stimulated conditions, with the possibility of revealing phenotypes not observed in resting conditions. This latter aspect is extremely fascinating, considering the possibility to precisely analyze several new genetically altered murine models (4). In this review we will first dissect the physiological mechanisms activated in the cardiovascular system by exercise training and the key parameters to be analyzed. We will next describe how the comparative analysis of cardiovascular function in wild-type (WT) and genetically modified mice can be extremely fascinating, considering the possibility to precisely analyze several new genetically altered murine models of human cardiovascular disease. The intensity-controlled treadmill exercise represents a well-characterized model of physiological cardiac hypertrophy because of its ability to mimic the typical responses to exercise in humans. In this review, we describe cardiovascular adaptations to treadmill exercise in mice and the most important parameters that can be used to quantify such modifications. Moreover, we discuss how treadmill exercise can be used to perform physiological testing in mouse models of disease and to enlighten the role of specific signaling pathways on cardiac function.

animal models; physiological hypertrophy

Cardiovascular Adapts to Exercise: Mice and Humans

Healthy humans develop several functional and structural changes in response to exercise, resulting in an increase of exercise capacity. For example, hearts from trained athletes show increments in ventricular chamber volumes and weights, cardiac output (CO), and contractile function (24). Thus an optimal murine model of physiological hypertrophy should be characterized by similar adaptations to allow adequate studies of the molecular mechanisms underlying these modifications. Treadmill running is a valuable instrument to recreate physiological hypertrophy in both male and female C57BL/6J mice undergoing long-term intensity-controlled treadmill running protocols (29). Indeed, after 4 wk of treadmill exercise, both sexes develop physiological cardiac hypertrophy, demonstrated by an increase in ventricular weights and cardiomyocyte dimensions and normal cardiac function and structure (29, 50). However, several differences need to be taken into account when translating to humans the results of studies performed in mice. First, for both heart rate and blood pressure, mice display a high variability related to routine activities, such as grooming or feeding, and to stresses, such as handling (10). The normal resting heart rate in awake, unrestrained mice is between

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CARDIOVASCULAR EFFECTS OF TREADMILL EXERCISE

450–600 beats/min and thus consistently higher than humans, with peak heart rates during maximal exercise as high as 840 beats/min (10, 30).

The possibility that conditioning to repeated exercise can occur in mice is demonstrated by the cardiovascular and metabolic adaptations occurring in exercised mice. Indeed, an increase in exercise capacity and maximal oxygen consumption (\(\dot{V}O_{2\text{max}}\)), as well as a lower serum lactate level at equivalent submaximal exercise workloads, has been described in mice after 12 wk of training (4). Furthermore, trained mice are characterized by resting bradycardia, improved baroreflex-mediated tachycardia, and increased tachycardia in response to methylatrpine, whereas the propanolol effect is notably reduced in this setting (9). These changes are likely related to an increased vagal and decreased sympathetic tone, similar to that seen in humans.

Humans and other large mammals present a vagal withdrawal responsible for the early heart rate enhancement and a sympathetic stimulation responsible for the subsequent gradual heart rate increase (61). Although mice seem to be characterized by a low-resting vagal tone because of the small tachycardic response to atropine (10, 68), the initial phase of the heart rate response appears related to vagal withdrawal, since \(\beta_1\)-adrenergic receptors (\(\beta_1\)-ARs) knockout (KO) mice still manifest this early tachycardic response but lack the later, more gradual increase (57). Similarly, the blood pressure response to an incremental treadmill protocol in mice is qualitatively comparable with that observed in humans and larger mammals (10).

In both mice and humans, exercise is the most critical physiological stimulus increasing myocardial oxygen demand. In contrast to humans and other large mammals, mice have significantly higher weight-corrected values of resting oxygen consumption (\(\dot{V}O_2\)) (10, 78). The increment in oxygen demands of the left ventricle during heavy exercise is met through an increase in the coronary blood flow, as hemoglobin concentration and oxygen extraction increase only modestly in most species (25). Coronary vascular adaptations in response to exercise training include structural changes (angiogenesis and vascular remodeling) and functional alterations of the vasomotor control (32–34). Given the technical difficulty of measuring coronary blood flow in small animals, few studies on coronary or myocardial blood flow responses to exercise in mice are currently available (25). However, left ventricles of trained mice show, only after a long-term exercise, an increased capillary density and a shorter intercapillary distance compared with the control group (69). Interestingly, treadmill exercise provides a more pronounced improvement in the capillarization of papillary muscles compared with the ventricular wall. This could depend on regional variations in the ventricular wall myocard hypertrophy and wall stress (69).

### Evaluation of Exercise Capacity in Treadmill Exercise Training

Several important parameters can be measured during treadmill exercise to evaluate the physiological responses to physical training (Table 1). First, it is possible to determine the exercise capacity, i.e., the maximal amount of exercise work achievable (9), that is usually quantified by several parameters such as the duration of exercise, workload achieved during exercise, heart rate and blood pressure increases, ECG parameters, \(\dot{V}O_2\), and carbon dioxide production (\(\dot{V}CO_2\)). The tissue \(\dot{V}O_2\) can be assayed using the important parameter \(\dot{V}O_2\) (\(\dot{V}O_2\) through ventilation). The measurement of \(\dot{V}O_2\) derives from the Fick equation: \(\dot{V}O_2 = CO \times (CaO_2 - CvO_2)\), where \(CaO_2\) is arterial oxygen content and \(CvO_2\) is venous oxygen content. \(\dot{V}O_2\) can be evaluated in both resting and exercising conditions, allowing an assessment of its modifications during training exercise. This latter evaluation provides one of the most significant metabolic parameters of aerobic exercise capacity, i.e., the \(\dot{V}O_2\text{max}\). This parameter corresponds to the point at which no further \(\dot{V}O_2\) enhancement is observable, despite increments in exercise intensity. Therefore, it represents the true metabolic limit to \(\dot{V}O_2\) (35, 47, 66).

An important blood parameter that can be measured during treadmill exercise is the lactate level. Blood lactate levels traditionally build as exercise intensity increases. The concentration of lactate in the blood is directly associated with exercise fatigue and has been long argued to be a contributing factor (62–64).

A further interesting measurement commonly used for exercise capacity evaluation is the anaerobic threshold, corresponding to the point at which energy production is widely dependent on anaerobic metabolism. Anaerobic threshold is calculated through the ratio of \(\dot{V}CO_2\) to \(\dot{V}O_2\), i.e., commonly called respiratory exchange ratio (RER) (10, 47, 66). Moreover, lactate levels have been used to assess the anaerobic metabolism (43), but this measurement is curbed by needing repeated measurements at different workload levels.

In addition to \(\dot{V}O_2\text{max}\) and RER, which are metabolic measurements, another common technique to evaluate exercise capacity consists of quantifying the “maximal duration” or the “maximal workload” defined as a sum of kinetic (\(E_k = m v^2/2\)) and potential (\(E_p = m g \cdot \nu \cdot r \cdot \sin \phi\)) energy of the mice on the treadmill, where \(m\) is animal mass, \(v\) is running velocity, \(g\) is acceleration due to gravity, \(r\) is elapsed time at a given protocol level, and \(\phi\) is the angle of inclination (79).

### Table 1. Most common parameters recorded during treadmill exercise in mice

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normal Values</th>
<th>References</th>
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<tr>
<td>Heart rate, beats/min</td>
<td>463 ± 13.0</td>
<td>4, 10, 35, 47, 66, 77</td>
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<tr>
<td>Blood pressure, mmHg</td>
<td>113 ± 8.0</td>
<td>10, 11</td>
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<tr>
<td>(\dot{V}O_2), ml·kg(^{-1})·min(^{-1})</td>
<td>46.9 ± 9.6</td>
<td>10, 26, 47, 66</td>
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<tr>
<td>(\dot{V}O_2\text{max}, ml·kg(^{-1})·min(^{-1})</td>
<td>112.3 ± 20.9</td>
<td>10, 26, 47, 66</td>
</tr>
<tr>
<td>(\dot{V}CO_2), ml·kg(^{-1})·min(^{-1})</td>
<td>37.3 ± 9.34</td>
<td>10, 26, 47, 66</td>
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<tr>
<td>Workload, beam breaks/min</td>
<td>14.1 ± 4.9</td>
<td>10, 21</td>
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<tr>
<td>Duration of exercise, min</td>
<td>19.2 ± 4.76</td>
<td>10, 21, 26</td>
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<tr>
<td>Blood lactate, mM</td>
<td>4.90 ± 0.34</td>
<td>17, 26</td>
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<tr>
<td>RER ((\dot{V}CO_2/\dot{V}O_2))</td>
<td>0.79 ± 0.05</td>
<td>10, 26, 47, 66</td>
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<tr>
<td>ECG, ms</td>
<td>5 ± 21, 77</td>
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<tr>
<td>PR interval</td>
<td>54.1 ± 13.7</td>
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<tr>
<td>QRS</td>
<td>30.0 ± 10.8</td>
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<tr>
<td>QT interval</td>
<td>109.4 ± 29.3</td>
<td></td>
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<tr>
<td>Maximal running speed (25° slope), m/min</td>
<td>23.4 ± 4.79</td>
<td>26</td>
</tr>
<tr>
<td>Maximal running distance, m</td>
<td>449.2 ± 8.18</td>
<td>26</td>
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</table>

Values are means ± SD. \(\dot{V}O_2\), \(O_2\) consumption; \(\dot{V}O_2\text{max},\) maximal \(\dot{V}O_2\); \(\dot{V}CO_2\), \(CO_2\) production; RER, respiratory exchange ratio; ECG, electrocardiogram.
Exercise Protocols

Exercise training induces cardiovascular and metabolic changes that are dependent on exercise intensity and duration. In most protocols, exercise training is performed on a motor treadmill at low-moderate intensity (50–70% maximal running speed) for 1 h/day, 5 days/week for 4 wk, with a gradual increase in speed from 0.3 to 1.2 km/h (Table 2). Usually, the animals are adapted to the procedure for 1 wk before beginning the exercise training protocol. After adaptation, the sedentary group is placed on the stationary treadmill three times a week to provide a similar environment. The animals undergoing this procedure usually show a linear increase in heart rate, $V_{O2max}$, and RER (9, 19, 29).

Confounding Factors

Several factors can bias the exercise procedures and thus the derived measurements. The comparison of the results in different studies is not always simple because of the possibility of differences regarding test protocols, equipment, body mass, strains, age, and sex and how accustomed the mice were to the methods. For instance, it has been demonstrated that mice strain (10, 38), ambient temperature (47), and age (65) influence $V_{O2max}$.

Among the potential confounding factors related to treadmill exercise in mice, one of the most important is represented by strain (27). Different inbred strains present substantial differences in exercise capacity, thus representing a critical issue when transgenic or KO mice are crossed to obtain animals with multiple genetic alterations (such as double KOs), with multiple strains contributing to the background. Furthermore, there are differences in exercise capacity between forced treadmill and voluntary wheel running protocols (10). These are amplified if different strains are considered: for example, C57BL/6J mice demonstrate one of the best exercise capacities on the voluntary wheel but one of the worst on the treadmill, whereas Dilute Non-Agouti (DBA) mice evidence one of the best capacity on the treadmill and the worst on the wheel (37). Strain differences have been also described for other metabolic parameters such as $V_{O2}$ and $V_{CO2}$ (10) and for peripheral vascular responses mediated by endothelium-dependent and -independent vasodilators (3).

Environment also has a substantial influence on murine cardiovascular parameters, although some of the influences that have the largest effect on resting parameters (e.g., state of arousal) are minimized during exercise. A low-level constant workload treadmill exercise can be used to reduce the influence of activity level and arousal state. Moreover, to avoid excessive handling of animals and to acclimate animals to the exercise apparatus, a thermoneutral environment should be maintained.

Acclimatization can be also achieved by placing mice in the treadmill for 10–20 min before starting exercise. In this way also the possible conditioning related to acute treadmill running exposure could be avoided. Exercise protocols should always be performed at the same time of day considering that mice are normally nocturnal animals. Controls and experimental subjects should be tested in tandem rather than sequentially to avoid the season influence on cardiovascular performance. Moreover, it seems still prudent not to mix females and males in the same study (4).

Another crucial variable is mice motivation, since substantial differences have been observed between exercise capacities derived from voluntary wheel running and treadmill exercise, in which running is motivated usually by an electric shock (37). Thus, although the shock stimulation represents one of the major advantages of treadmill running, together with the ability to precisely regulate work intensity and the possibility to apply uniform exercise workloads to all experimental animals, it can induce mental stress. Moreover, with the use of treadmill exercise, not only is the shock stimulation important but also the acclimatization of animals to the running apparatus, which can be obtained by placing the mouse in the treadmill for 10–20 min before the onset of exercise.

Forced swimming has also been a commonly used tool in assessing exercise capacity in mice, especially because motivation is less of a problem than with treadmill exercise. Exercise responses to swimming are quite different from those to treadmill running, complicated by factors such as the diving reflex and episodes of hypoxia associated with diving (8, 16). During chronic swimming exercise, we previously reported increased heart weight-to-body weight ratios and decreased heart rates with normal cardiac function (50). When compared with treadmill exercise, the swimming protocol results in submaximal levels of exercise intensity with lower peak heart rate, $V_{O2max}$, and cardiac hypertrophy development (4, 50). The advantages of swimming protocols include the relative ease with which it is possible to induce mice to swim compared with running on a treadmill and the simplicity and minimal expense of the equipment required. The disadvantages of swimming include the lack of graded workload protocols and the difficulty of measuring cardiovascular parameters and quantifying exercise intensity.

Treadmill Exercise in Genetically Modified Mice: Evidence from the Adrenergic System

It is generally accepted that regular physical activity induces beneficial effects on the cardiovascular system, and these are
often associated with a reduction in the sympathetic nervous system activity and activation of ARs (9). Treadmill exercise has been used in several different strains of genetically modified mice to determine the role of specific signaling pathways in the regulation of cardiovascular functions (Table 3). In particular, genetically modified mouse models altering the expression of specific components of the adrenergic system have been among the first models to be used in which a treadmill has been used to detect subtle abnormalities in exercise capacity (49, 51, 54).

The release of epinephrine (Epi) from the adrenal medulla is among the first responses to many pathological or physiological stressors, including dynamic exercise. To investigate the role of Epi in regulating cardiovascular function at rest and with stress, an Epi-deficient mouse model [phenylethanolamine N-methyltransferase KO mice (PNMT KO)] has been used (2). The total loss of Epi in PNMT KO mice had little influence on resting cardiac function, including heart rate, blood pressure, and ejection fraction, suggesting that Epi is not crucial in regulating cardiovascular function at rest (2). In response to treadmill exercise, the positive cardiac chronotropic was similar in WT and PNMT KO mice (2). In contrast, treadmill exercise caused a higher increase in blood pressure in PNMT KO mice, suggesting that Epi-induced vasodilation is required to prevent blood pressure overshoot during exercise (2).

Given the important role that β-ARs play in the regulation of blood pressure, cardiac chronotropy, isotropy, and metabolism, the β1-AR KO mice have been the first KO mouse model to receive a complete cardiovascular analysis following treadmill

<table>
<thead>
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<th>Table 3. Examples of treadmill exercise in genetically modified mice</th>
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<tr>
<td><strong>Mouse Strains</strong></td>
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<tr>
<td>β1-Adrenergic receptor KO mice (β1-AR KO)</td>
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<tr>
<td>β2-Adrenergic receptor KO mice (β2-AR KO)</td>
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<tr>
<td>βββ-β2-Adrenergic receptor double-KO mice (βββ-β2-AR KO)</td>
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<tr>
<td>Phenylethanolamine N-methyltransferase KO mice (PNMT KO)</td>
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<td>Phospholamban KO mice (PLB KO)</td>
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<tr>
<td>K\textsubbox{ATP} channels KO mice (Kir 6.2 KO)</td>
</tr>
<tr>
<td>AMPK-β2 KO mice (AMPK-β2 KO)</td>
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<tr>
<td>Endothelial nitric oxide synthase KO mice (eNOS/- KO)</td>
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<tr>
<td>Calponin KO mice (Calponin/- KO)</td>
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<tr>
<td>Taurine transporter KO mice (taut/- KO)</td>
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<tr>
<td>Muscle glycogen synthase KO mice (MGS/- KO)</td>
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<tr>
<td>Estrogen receptor-β KO mice (ER-β KO)</td>
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<tr>
<td>Glucose transporter-4 KO mice (GLUT4/- KO)</td>
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<tr>
<td>Dystrophin-deficient mice (mdx)</td>
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<tr>
<td>Adenyl cyclase 8 TG mice (TG AC8)</td>
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<td>Adenyl cyclase 5 TG mice (TG AC5)</td>
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<tr>
<td>Ventricular myosin regulatory light chain-2 TG mice (TG MyLC2v)</td>
</tr>
<tr>
<td>Myosin-binding protein C lacking 9 amino acids (99) TG mice (TG MyBP-C99)</td>
</tr>
<tr>
<td>Myosin-binding protein C-mutated TG mice (TG MyBP-Cm1)</td>
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<tr>
<td>α-Myosin heavy chain arginine-403 glutammmutated TG mice (TG α-MyHC R403Q)</td>
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<tr>
<td>K\textsubbox{ATP} channel-mutated TG mice (TG Kir 6.1-AAA or Kir 6.2-AAA)</td>
</tr>
<tr>
<td>Sodium-calcium exchanger-1 TG mice (TG NCX1)</td>
</tr>
<tr>
<td>α-RNA 499 TG mice (TG miR-499)</td>
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</table>

KO, knockout; WT, wild-type; RER, respiratory exchange ratio; TG, transgenic; K\textsubbox{ATP}, ATP-sensitive K⁺ channel.
exercise (56). Although these mice displayed a considerable reduction of exercise-induced tachycardia, they exhibited exercise abilities and exercise-induced enhancement of VO2 and CO2 similar to WT mice (55). It is presumable that to maintain normal VO2, these animals displayed an increase in the stroke volume, principally because of adaptations in peripheral vascular resistance and venous return, and to the lower heart rates that would allow for the increase in diastolic filling time and stroke volume through the Frank-Starling mechanism (55).

Treadmill exercise tests have also been performed in mice with targeted deletions of the β2-AR (7) or KO for both β1- and β2-ARs (55). β2-AR KO mice display normal resting heart rate and blood pressure, can exercise normally, and actually have a greater total exercise capacity a lower RER than WT mice at comparable workloads, suggesting a difference in the metabolic state and substrate utilization (7). In addition, β2-AR KO mice become hypertensive during exercise, suggesting that the catecholamine release promoted by exercise might lead to unopposed stimulation of α1-ARs and vasoconstriction in these mice.

Despite the total absence of both β1- and β2-ARs, β1/β2 double-KO mice present basal heart rate, blood pressure, and metabolic rate similar to WT mice. These results are somewhat surprising, considering the large number of pharmacological studies using nonselective or selective β-AR antagonists to lower heart rate and blood pressure. It is possible to speculate that genetically modified mice lacking any given receptor from the very early developmental stages might undergo compensatory alterations, becoming different from WT animals that are treated at a certain time of their adult life. Indeed, the regulation of alternative signals (for example, originated by muscarinic receptors or β3-ARs) might control such critical physiological functions when β1/β2-AR signaling is missing (55). However, treadmill exercise determines significant impairments in chronotropy, vascular reactivity, and metabolic response to exercise in these mice (55). Interestingly, although β1/β2 double-KO mice display reduced metabolic demands, these abnormal responses to exercise do not impact their maximal exercise capacity (55). Taken together, these studies indicate that whereas β1-ARs primarily control heart rate and contractility and β2-ARs mediate vasodilatation, other functions, such as the metabolic rate, are redundant, and deficiencies are not apparent until both AR subtypes are knocked out.

The loss of responsiveness to β-agonist stimulation is considered a fundamental hallmark of human failing hearts (6, 14, 28, 52, 73), resulting from the desensitization of β-ARs and the downregulation of multiple components of the β-AR system including the receptors themselves and adenylyl cyclase (AC), particularly the AC6 subtype (12, 53). Increasing evidence suggests that the normalization of β-AR signaling, including AC6 overexpression, consistently ameliorates cardiac dysfunction in rodents (59, 60) and large animal models of human heart failure (31). To test the effects of the cardiac upregulation of AC, several groups including ours have generated different transgenic mice with cardiac-restricted overexpression of AC isoforms, including AC5 (70, 71), AC6 (23), and AC8 (39). Surprisingly, whereas AC overexpression consistently results in an enhancement of cAMP production, the effects on basal cardiac contractility are somewhat controversial (36). Whether such variability in contractility detected in transgenic overexpression models would rely on isoform-specific properties was unknown. Moreover, whether increasing cAMP production in the heart would in turn translate into an increased functional capacity was unclear. Thus, to address these issues, we previously studied transgenic mice with cardiac-specific overexpression of either AC5 or AC8 and determined their intrinsic systolic and diastolic cardiac function and exercise performance (13).

Basal noninvasive cardiac evaluation in conscious WT and AC5/8-overexpressing mice failed to reveal significant differences between WT and transgenic mice. However, pressure-volume loop analysis showed that the intrinsic contractile state of the ventricle was significantly higher in both AC5 and AC8 mice compared with WT mice, and it was even higher in AC8 compared with AC5 mice (13). Interestingly, both AC5 and AC8 mice also showed an enhanced exercise capacity, with a need for less external stimuli compared with their WT littermates and with a significantly longer distance run (13). Whereas AC8 mice displayed a better performance to run at any speed analyzed, in AC5 mice the ability to run was increased only at fast belt speed compared with WT mice. Taken together, these data show that exercise training by treadmill is a powerful tool to magnify even subtle changes in cardiac phenotype of genetically modified mice, undetectable under basal conditions.

Conclusions

Treadmill exercise has emerged as a valuable instrument to study cardiovascular responses to stress in several genetically altered murine models of human cardiovascular disease and to understand the mechanisms of training-induced amelioration of cardiac function, thus representing a valuable tool to discover new molecular targets for the prevention and treatment of cardiovascular disease.

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H198 CARDIOVASCULAR EFFECTS OF TREADMILL EXERCISE

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