Exercise training improves cardiac function and attenuates arrhythmia in CPVT mice

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CPVT mice

MATERIALS AND METHODS

Experimental Protocol

Animal studies. The animal experiments conformed to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH publication no. 85-23, revised 1996) and was approved by the institutional animal care and use committee of Tel Aviv University (M-10-004). The murine model for the recessively inherited CPVT was previously described (40). Mutant and wild-type (WT) SvEv mice were maintained and bred in a facility and handled in accordance with the Guide for the Care and Use of Laboratory Animals. All animals were used in the present study at 6–9 weeks of age. The mice were housed in individual cages, and the room temperature was maintained at 22 ± 2°C. The animals were given a standard feed and water ad libitum. The experimental protocol was approved by the institutional animal care and use committee of Tel Aviv University (M-10-004). The murine model for the recessively inherited CPVT was previously described (40). Mutant and wild-type (WT) SvEv mice were maintained and bred in a facility and handled in accordance with the Guide for the Care and Use of Laboratory Animals. All animals were used in the present study at 6–9 weeks of age. The mice were housed in individual cages, and the room temperature was maintained at 22 ± 2°C. The animals were given a standard feed and water ad libitum.

Exercise is discouraged for patients who suffer from CPVT and carry one of the causative gene mutations. Abstaining from physical activity in young individuals may lead to considerable functional, social, and medical disadvantages. Exercise rehabilitation is currently recommended for patients postmyocardial infarction and those suffering from congestive heart failure (9, 23). It was shown to improve the functional state and the general well-being and possibly has a positive effect on cardiac function and longevity (11, 23, 30). Yet the effect of long-term exercise training in primary arrhythmic disorders, in particular those manifested as exercise-induced arrhythmia, is unknown.

CPVT is associated with high risk of VT and ventricular fibrillation secondary to increased sympathetic drive and catecholamine release. One of the methods to antagonize these is to reduce sympathetic reflexes while increasing the vagal tone. Therefore, exercise could benefit CPVT patients through increased vagal tone, decreasing the sympathetic drive and/or the increased expression of calcium-handling proteins, as shown by Billman and colleagues (1, 2) and other investigators (4, 25). On the contrary, recurrent exposure to exercise-induced arrhythmia could lead to the development of tachycardia-induced cardiomyopathy and/or exacerbate the disease phenotype.

Our laboratory has previously described mice homozygous for CASQ2 null-allele that suffer from typical arrhythmia and develop mild cardiomyopathy attributed to abnormal calcium handling (40). In the present study, we evaluate the effect of exercise training on heart rate, arrhythmia severity, exercise capacity, and heart function in young animals with CPVT2.

CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA (CPVT) is a malignant ventricular arrhythmia, evoked by emotional or physical stress, which can lead to syncope, convulsions, and sudden death. The arrhythmia appears to be mediated by abnormal calcium release from the sarcoplasmic reticulum (SR), evoking delayed after-depolarizations, and commencing in bidirectional or polymorphic ventricular tachycardia (VT) (8). Heterozygous mutations in the cardiac ryanodine receptor 2 and recessively inherited mutations in the calsequestrin gene (CASQ2) constitute the molecular cause in the majority of patients with CPVT and in their affected family members (14, 19, 24). The first-line therapies are β-adrenergic blockers, but they fail to prevent arrhythmia in a substantial minority of patients. These individuals require additional therapies, such as flecainide, calcium channel blockers, implantable defibrillator, and eventually sympathetic denervation (36, 46).

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pathogen-free facility on regular rodent chow, with free access to water and 12:12-h light and dark cycles.

Male WT and CASQ2ΔΔ [knockout (KO)] mice were randomly assigned at 8 wk of age to four groups: WT sedentary, WT exercise training, KO sedentary, and KO training.

Mice from exercise groups underwent training on a motorized rodent treadmill (Exer-6M; Columbus Instruments, OH) with an adjustable speed and a slope of 5°. Our protocol included 2 wk of gradual habituation, followed by 4 wk of intense training. During the first week, the mice exercised 3 days/wk, 30 min/day, at a speed of 8, 10, and 12 m/min, respectively. During the second week, the mice exercised 3 days/wk, 60 min/day, at a speed of 10, 12, and 15 m/min, respectively. Thereafter, mice were forced to run for 60 min/day at 15 m/min, 5 days/week, for 4 wk (5, 38).

Following completion of the training protocol, all mice underwent echocardiography, assessment of maximal exercise capacity, and implantation of a telemetry device. After 24 h to recover from surgery, mice were tested for susceptibility to catecholamine-induced arrhythmia.

**Procedures**

**Murine telemetry transducer.** Murine telemetry transducer (DSI, St. Paul, MN, device weight 3.8 g) was surgically implanted under the skin on the back of the animal, as previously described (36). Mice were anesthetized with ketamin 75–90 mg/kg and xylazine 5–8 mg/kg ip (Kepro).

Two-dimensional (2D) and M-mode echocardiography was performed using an echocardiogram (Visual, Sonix) equipped with a 30-MHz linear transducer. Animals were lightly anesthetized with inhalation of isoflurane (Terrell, TX). 2D parasternal short-axis imaging of the heart was performed. An M-mode cursor was positioned perpendicular to the interventricular septum and posterior wall of the left ventricle (LV) at the level of the papillary muscles. An M-mode image was obtained at a sweep speed of 100 mm/s. Diastolic and systolic LV wall thickness, LV end-diastolic dimensions, and LV end-systolic chamber dimensions were measured. Left ventricular end-diastolic and end-systolic area were obtained from the 2D parasternal short-axis view. The LV fractional shortening and LV fractional area change were calculated.

To determine the maximal exercise capacity, mice were placed on the treadmill at the speed of 7.5 m/min with a 5° slope. The speed was increased by 2.5 m/min every 3 min up to 25 m/min, followed by increasing the slope to 15°. The mouse was then left to run until the limit of its capacity to follow the track. The total exercise duration was measured.

**Provocation testing for CPVT susceptibility.** Mice were subjected to exercise test and then to intraperitoneal injection of epinephrine, as previously described (20, 40). In brief, baseline telemetry was recorded at rest in caged sedentary animals with no stressful stimuli. Then mice were then moved to a rodent treadmill. The treadmill speed was gradually increased over 2 min from 5 to 8 m/min at a 5° slope. Heart rhythm recording was obtained during the last 30 s of this stage, at a speed of 8 mm/s. The animal was then forced to run at 15 m/min. The ECG was continuously recorded during the last 10 s of this “sprint” and the subsequent 60 s of recovery. After 5 min of rest, mice were injected with epinephrine (0.5 mg/kg ip), followed by 5 min of continuous telemetric monitoring.

**Quantitative real-time PCR.** Total RNA was purified from hearts using TRIzol method (Ambion, Austin, TX), according to the manufacturer’s instructions. The quantity of total RNA was determined by OD260 measurements. cDNA was synthesized from total RNA using the TaqMan High Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Foster City, CA), according to the manufacturer’s protocol. Quantitative real-time PCR analysis for mouse atrial natriuretic peptide (ANP) [natriuretic peptide precursor A (NPPA)], brain natriuretic peptide (BNP) [natriuretic peptide precursor B (NPPB)], assembly inducing protein (ACTA), and connexin 43 (CX43) was performed using the ABI 7000 Sequence Detection system (Applied Biosystems). The primers and TaqMan FAM probes were ordered from Applied Biosystems. A total of 2 μl of cDNA was amplified with 10 μl TaqMan Universal PCR MasterMIX. 1 μl TaqMan SNP genotyping assays, and 7 μl diethyl pyrocarbonate. PCR amplification was performed in triplicate. The average cycle threshold was normalized to endogenous control gene, mouse TATA-box. Stability of TATA expression across the experimental groups was verified by assessing its own expression relative to another constitutively expressed gene, β-actin (ACTB).

**Western blot analysis.** Whole ventricles were homogenized in RIPA buffer. The total homogenate was centrifuged at 8,000 RPM for 10 min at 4°C. The supernatant was collected, and the total protein levels were quantified by the Bradford reagent (Sigma, St. Louis, MO), with bovine serum albumin as a standard.

**Protein** (30 μg/lane) was separated on 10% SDS-polyacrylamide gel under denaturing conditions and was transferred to a nitrocellulose membrane. The membrane was blocked by incubation for 2 h in 5% nonfat milk in Tris buffer containing 0.05% Tween 20 and then was immunoblotted overnight at 4°C with rabbit polyclonal antibodies against β-adrenergic receptor (β-AR) (Santa Cruz Biotechnology), sodium calcium exchanger (NCX) (R&D Systems, Minneapolis, MN), L-type calcium channel (LTCC), Na-K-ATPase, CX43 (Santa Cruz Biotechnology), and CASQ2 (Affinity Bioreagents, Golden, CO). Proteins were detected using a horseradish peroxidase-conjugated secondary antibody with ECL detection kit (Santa Cruz Biotechnology) and quantitated by densitometry.

**Statistical Analysis**

Results are expressed as means ± SD for continuous variables and categorically for arrhythmia prevalence. Heart rate and ventricular arrhythmia were analyzed manually from computer electrogram recordings and defined as follows: nonsustained VT, four or more consequent ventricular complexes; sustained VT, a VT lasting ≥15 s; monomorphic VT, a continuous ventricular rhythm with one predominant morphology; bidirectional VT, a ventricular rhythm with two predominant alternating morphologies; and polymorphic VT, a ventricular rhythm having at least three alternating morphologies. For purposes of statistical comparison, an animal having nonsustained VT or sustained VT under any condition was accepted as positive for VT. All other ventricular arrhythmias were defined as premature beats (premature ventricular complexes (PVCs)), ventricular bigeminy, and complex PVCs (salvos, couplets, and triplets).

The results of real-time PCR were expressed per each sample as relative quantification calculated as 2−ΔΔCT. Protein levels were normalized for GAPDH or ACTB expression and expressed as a ratio of density values. A statistical difference between the groups was assessed using Student’s t-test and the ANOVA using the multiple-comparison option of Duncan and χ2/Fisher exact test, as appropriate. Two-tailed P < 0.05 was accepted as statistically significant.

**RESULTS**

**Comparison of Sedentary KO and WT Mice**

Echocardiography of 15-wk-old animals showed a decrease in systolic function in KO mice and an increase in the LV size, as manifested by measurement of end-systolic and end-diastolic cross-sectional area in the short-axis view (Table 1). There were no significant differences in the LV wall thickness, but the heart-to-body weight ratio was higher in the KO mice (Fig. 1, P < 0.05).

Under resting conditions, KO mice had a lower sinus heart rate compared with WT mice (562 ± 134 vs. 732 ± 59 beats/min, P < 0.05) and often exhibited complex ventricular
Table 1. Echocardiographic studies before and after 6-wk exercise training of WT and KO mice

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>HR, beats/min</th>
<th>IVS, mm</th>
<th>PW, mm</th>
<th>LVEDD, mm</th>
<th>LVEDD, mm</th>
<th>FS, %</th>
<th>2D ESA, mm²</th>
<th>2D EDA, mm²</th>
<th>LVFAC, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT sedentary</td>
<td>5</td>
<td>428 ± 36</td>
<td>1.1 ± 0.1</td>
<td>0.9 ± 0.1</td>
<td>1.6 ± 0.3</td>
<td>3.2 ± 0.3</td>
<td>50.9 ± 7.3</td>
<td>2.4 ± 1.3</td>
<td>7.9 ± 1.6</td>
<td>69.8 ± 12.0</td>
</tr>
<tr>
<td>WT trained</td>
<td>9</td>
<td>422 ± 36</td>
<td>1.0 ± 0.1</td>
<td>0.9 ± 0.1</td>
<td>1.6 ± 0.4</td>
<td>3.2 ± 0.4</td>
<td>50.7 ± 8.7</td>
<td>2.4 ± 1.2</td>
<td>8.4 ± 2.1</td>
<td>71.7 ± 8.8</td>
</tr>
<tr>
<td>KO sedentary</td>
<td>5</td>
<td>470 ± 84</td>
<td>1.0 ± 0.1</td>
<td>0.9 ± 0.1</td>
<td>2.5 ± 0.2</td>
<td>3.7 ± 0.3</td>
<td>33.1 ± 4.6* #</td>
<td>4.6 ± 1.0* #</td>
<td>10.9 ± 2.0* #</td>
<td>57.4 ± 8.9</td>
</tr>
<tr>
<td>KO trained</td>
<td>7</td>
<td>439 ± 59</td>
<td>1.0 ± 0.1</td>
<td>0.8 ± 0.1</td>
<td>1.8 ± 0.5</td>
<td>3.2 ± 0.5</td>
<td>43.2 ± 12.3</td>
<td>2.9 ± 1.4</td>
<td>7.4 ± 2.2</td>
<td>61.1 ± 13.1</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, no. of mice. WT, wild type; KO, knockout; HR, heart rate during light anesthesia; IVS, interventricular septum; PW, posterior wall; LVEDD, left ventricular end-diastolic dimension; LVEDS, left ventricular end-systolic dimension; FS, fractional shortening; 2D ESA, end-diastolic area on two-dimensional echo; 2D EDA, end-diastolic area on two-dimensional echo; LVFAC, left ventricular fractional area change. *P < 0.05 vs. KO trained. #P < 0.01 vs. WT sedentary.

The exercise capacity was impaired in KO mice, as manifested by significantly decreased duration of the maximal treadmill exercise test (Fig. 2).

Hearts from KO mice had a significant increase in the BNP gene expression associated with myocardial dysfunction (see Fig. 4). There was no significant difference in the expression of ANP, CX43, and α-skeletal actin.

CASQ2 protein was absent from the homozygous KO mice studied. There were no differences between KO and control mice in the levels of CX43, NCX, Na-K-ATPase, LTCC, and β1-AR, proteins that were assumed to play a potential role in calcium handling and CPVT (see Fig. 5).

Effects of Exercise Training in KO Mice

Two mice from KO exercise group and three mice from the WT exercise group did not complete the training protocol. They were not able to continuously run for 1 h and were excluded. There was no mortality during the training period.

Exercise training led to a significant decrease in the basal heart rate in controls, but not CASQ2 KO mice (Table 2). There was no change in heart dimensions or function determined by echocardiography in WT mice. Exercise training improved the mean fractional shortening of KO mice from 33 to 43% (P < 0.05), while the LV cross-sectional end-systolic area and end-diastolic area became significantly lower than in sedentary KO mice (Table 1). Remarkably, after training, echocardiographic measures in mutant mice became comparable to that of the WT animals.

Concomitantly, trained KO mice, but not WT controls, exhibited a significant increase in their exercise endurance compared with sedentary mice (Fig. 2).

The arrhythmia severity in trained KO mice was lower than in sedentary KO under resting conditions (P < 0.05, Table 2). However, during exercise stress and epinephrine injections, i.e., provocation testing for CPVT, the arrhythmia severity was similar to that of sedentary KO (Table 2). We further assessed the arrhythmia load by counting the number of abnormal ventricular complexes during peak exercise. As can be seen in Fig. 3, the ventricular premature beat count was significantly lower in trained compared with sedentary KO mice (P < 0.05).

Following exercise conditioning, there was a significant decrease in the expression of BNP mRNA in KO mice compared with the sedentary group. A similar trend was found in the expression of the gene of ANP (P = 0.07, Fig. 4). Training was also associated with a trend for a decrease in the β1-AR, which was, in particular, pronounced in the KO mice (Fig. 5, P = 0.08). The levels of other proteins studied, CX43, NCX, Na-K-ATPase, and LTCC, did not change in either group following exercise conditioning (data not shown).

DISCUSSION

CPVT is manifested by lethal ventricular arrhythmia evoked by physical or emotional stress. Recessively inherited CPVT2 is caused by either missense or null-allele mutations in the cardiac CASQ2 gene. It has been suggested that defects in CASQ2 cause protein deficiency, impairing Ca²⁺ uptake to the SR and Ca²⁺-dependent inhibition of ryanodine channels, thereby leading to diastolic Ca²⁺ leak, delayed after-depolarizations, and arrhythmia (19). CASQ2-deficient murine models were also reported to be associated with mild cardiomyopathy (40). While acute physical stress is known to be potentially lethal in CPVT patients (14), the effect of repeated mild-to-moderate exercise has not yet been studied in depth. In this study, we examined the effect of exercise training on LV remodeling and arrhythmia in CASQ2 KO mice compared with WT.

Exercise training improves symptoms in chronic heart failure and has numerous beneficial effects of cardiovascular and skeletal muscle function (9, 13, 29). An increase in calcium sensitivity has been associated with improvement in heart function (25, 35). In one study, running exercise protected transgenic mice from developing heart failure attributed to sympathetic hyperactivity, probably due to the upregulation of calcium-handling proteins and improving in SR calcium re-uptake (35). Exercise has been tested also in animal models of human arrhythmia. In 1978, McElroy et al. (28) demonstrated protection against ischemia-reperfusion damage. They found that regular swimming training causes a decrease in infarct size in rats. Exercise training in dogs subjected to myocardial infarction resulted in fewer episodes of VT, as well as in...
increased capability to withstand arrhythmic episodes, attributed to a decrease in β-ARs in the heart (1, 2). The effect of exercise training on the myocardium and the autonomic nervous system has been extensively investigated (4, 21, 31, 39).

The findings of these studies have shown a decrease in the sympathetic activity and/or an increase in the parasympathetic nervous system has been extensively investigated (4, 21, 31, 39). While the exact signaling pathway causing this phenomenon is not fully understood, exercise does affect myocardial dysfunction and are a useful prognostic indicator in human and in animals, manifesting as a decrease in the resting heart rate and in blood pressure (2, 12, 32, 38). While the exact signaling pathway causing this phenomenon is not fully understood, exercise does affect myocardial gene expression and protein levels (18). An increase in the myosin heavy chain, sarco(endo)plasmic reticulum Ca2+-ATPase, and phospholamban expression was demonstrated after 13 wk of intensive training in rats (18, 47). Others have reported a decrease in the natriuretic factor A, skeletal actin ATPase, and phospholamban expression was demonstrated following exercise training (3, 12, 16, 37). While differences between the studies could result from protocol duration and intensity, none of these studies found a change in the β-receptor affinity.

Our study is the first report documenting the effect of exercise training on the severity of arrhythmia and exercise capacity in a mouse model of CPVT. The in vivo outcomes comprised heart rhythm disturbances, endurance, and echocardiography measures after a 6-wk training protocol. Selected gene and protein expression has been examined in cardiac extracts. Sedentary KO mice had decreased systolic function, an increase in the LV size, and a higher heart/body weight ratio compared with WT controls (Fig. 1). The exercise capacity was impaired in KO mice (Fig. 2), and cardiac gene expression showed an increase in the BNP gene, which is associated with myocardial dysfunction (Fig. 4). BNP secretion is regulated by the cardiac chamber wall stretch and correlates with cardiac filling pressure (26, 41). High levels of BNP indicate cardiac dysfunction and are a useful prognostic indicator in CPVT.
The activity of the sympathetic system could constitute the link between the effects of exercise training and arrhythmia in a murine model of CPVT2. The expression of β-AR is a major determinant of cardiac function and ventricular arrhythmia in heart failure, cardiomyopathy, and arrhythmic disorders. Our results show a modest effect of exercise training on reducing β-AR expression, which was more pronounced in CASQ2-deficient mice. A decrease in β-AR has previously been described after dog training in association with attenuating malignant arrhythmia (34, 39, 45). We believe that decreased sensitivity to catecholamine stimulation in animals suffering from CPVT led to a decreased arrhythmia load and contributed to improvement in LV function. A training protocol longer than 6 wk and functional assessment of β1-AR activity could show even larger benefits.

Exercise training had a very pronounced differential effect on the resting heart rate. As could be expected, heart rate decreased in trained WT mice. Conversely, KO mice have a low resting heart rate, which is a part of the disease phenotype (19, 22, 40), but their heart rate increases after training (Table 2). These divergent responses suggest a profound difference in the activities of either calcium clock or autonomic nervous system, which are not adequately explained by β1-AR expression. Since we found no change in the expression of NCX, Na-K-ATPase, and LTCC, proteins that are involved in calcium handling and could mediate the effect of exercise training on cardiac rhythm and function, the putative mechanism remains to be identified (44, 48).

**Limitations**

Mice with CASQ2 KO develop cardiomyopathy, and their improved endurance may be attributed to improved LV function with exercise. Because human CPVT patients have no structural heart disease, their benefit from training might be more limited. Furthermore, mice with CPVT causing mutations recapitulate the arrhythmic phenotype, but do not suffer from sudden death. Humans with CPVT would necessarily receive β-blockers and require continuous monitoring during exercise.

**Post-myocardial infarction, cardiomyopathy, and heart failure patients.**

As opposed to humans with CPVT, ventricular arrhythmia is rather prevalent in CASQ2 KO mice, even at rest (Table 2), possibly due to stressful stimuli in the external environment. Ventricular arrhythmia present at rest could contribute to development of contractile dysfunction through a mechanism resembling tachycardia-induced cardiomyopathy. Noteworthy, the phenotypic alterations in CASQ2 KO mice were not associated with altered expression of either a CX43 gene or its protein (10, 17). We postulate that these mice develop cardiomyopathy due to a detrimental combination of frequent ventricular arrhythmia and abnormal calcium handling.

Exercise training in KO mice was associated with neither mortality nor arrhythmia exacerbation. It led to decreased arrhythmia load at rest and during exercise. While we found no difference in stress-induced VT prevalence, trained KO had less VT at rest and fewer PVCs at peak exercise points compared with sedentary KO. At the end of the training protocol, they demonstrated a significant improvement in LV function and exercise capacity. The improvement in cardiac function was paralleled by a reduction in natriuretic gene expression (Fig. 4). We postulate that better cardiac function and less rhythm disturbances account for improved exercise capacity in trained KO mice. The impact of CASQ2 deficiency in fast skeletal muscle and the role of muscle conditioning deserve a further study (33). The WT mice were not significantly affected by exercise. Because the training protocol was adjusted according to the running speed of KO mice, the exercise intensity (at most 15 m/min) was rather mild for normal animals. Apparently, exercise adaptation was less pronounced in healthy animals due to inadequate training volume (3, 15).
β-Blockers could blunt the effect of training by upregulating the level of β-receptors. Our study was performed without β-blockers, because those were found to be ineffective against CPVT in CASQ2 mice (20). Importantly, β-blockers should not be expected to abolish cardiac and autonomic adaptation to exercise training in humans and rodents (6, 27, 43).

Provocation testing for CPVT susceptibility by injecting epinephrine introduces an artificial element and blood pressure elevation, which might prevent correct assessment of adaptation to exercise. However, the results of testing with epinephrine paralleled the results of exercise stress testing (Table 2). It is still possible that we underestimated some of the benefits of exercise conditioning, either because of inadequate training, or because of using crude and categorical methods to define arrhythmia. Measurement of the sympathetic nervous activity and vagal tone could provide further insights on the effect of training on the autonomic system in CPVT mice.

In conclusion, while competitive sports and strenuous exercise are hazardous and shall be prohibited in CPVT patients, low- to moderate-level exercise training may, in fact, be beneficial. In mice, it improves cardiac function and exercise capacity and seems to decrease arrhythmia load without increasing arrhythmia severity. Drug and device therapy, combined with exercise training, may have a synergistic protective effect. Hence, supervised exercise rehabilitation programs should be carefully investigated for their potential to optimize the care of patients with CPVT and other arrhythmic disorders.

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GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


