

# Follow-Up with Exercise Test of Effort-Induced Ventricular Arrhythmias Linked to Ryanodine Receptor Type 2 Gene Mutations

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The aim of this study was to assess exercise test results and efficacy of therapy with a  $\beta$  blocker (acebutolol) in ryanodine receptor type 2 (RyR2) mutation carriers with documented ventricular arrhythmias (VAs) and long-term follow-up. Twenty RyR2 mutation carriers belonging to 8 families and regularly followed at our center were analyzed using a study protocol involving electrocardiography, exercise tests off and on  $\beta$ -blocker therapy, 2-dimensional echocardiography, and signal-averaged electrocardiography. Off-therapy exercise testing triggered the onset of VAs at different heart rates (mean  $132 \pm 13$  beats/min) with various patterns that worsened while exercising and disappeared immediately after stopping. The most severe VAs detected were nonsustained ventricular tachycardia in 35% and ventricular couplets in 35%. In the remaining subjects single ventricular premature beats were recorded. In 15% of patients single monomorphic ventricular premature beats were detected and identified to be linked to RyR2 mutations owing to the presence of sudden deaths of their family members and subsequent family screening. Acebutolol made the VAs disappear completely in 20% of subjects and decreased their complexity in 50%, whereas it did not change VAs appreciably in 30% of patients with less complex VAs. After  $11 \pm 8$  years of follow-up 2 patients developed syncope. In conclusion, exercise testing was a fundamental tool for assessing the clinical phenotype and efficacy of therapy in RyR2 mutation carriers and therapy with acebutolol led in most subjects to a decreased complexity of the arrhythmic pattern or to complete suppression.

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Ryanodine receptor type 2 (RyR2) has a pivotal role in regulating excitation–contraction coupling and sinoatrial node function.<sup>1–4</sup> RyR2 mutations alter channel activity at adrenergic activation, increasing the likelihood of spontaneous calcium release during diastole, which is the basis for triggered and polymorphic ventricular arrhythmias (VAs).<sup>5–8</sup> The main clinical entity is the catecholaminergic polymorphic ventricular tachycardia (VT), a highly malignant arrhythmogenic disorder prevalently present in a structurally normal heart, which is an important cause of sudden death in children and young adults.<sup>9–18</sup> Exercise triggers the onset of a broad spectrum of VAs that progressively worsen, usually leading to a highly reproducible polymorphic or bidirectional VT that fades on stopping

exercising.<sup>18–22</sup> The aim of our study was to analyze exercise test findings in a group of RyR2 mutation carriers developing VAs while they were off and on  $\beta$ -blocker therapy and study the efficacy of a  $\beta$  blocker (acebutolol) over a lengthy follow-up.

## Methods

From a cohort of 8 families (39 RyR2 mutation carriers) we selected 20 patients who carried 7 different RyR2 mutations, developed VAs during exercise testing, and were being monitored regularly. Silent mutation carriers (10 subjects without VAs during follow-up) and subjects with incomplete follow-up (9 subjects) were excluded. Our patients were heterozygous for RyR2 mutations: 6 carried the N2386I, 6 the A2387P, 2 the Y2392C, 2 the A77V, 2 the L433P, 1 the R420W, and 1 the M4504I. All mutations have been reported previously.<sup>9,12,17,23</sup> Two patients were index cases identified with exercise testing before participation during a screening for competitive sports, and the remaining subjects were discovered through family screening because of a positive family history of sudden death during effort or emotion (13 subjects, mean age  $19 \pm 5.7$  years). All subjects underwent electrocardiography, exercise testing,

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Table 1  
Comparison between exercise stress test off therapy and on therapy (at first evaluation and last follow-up)

Variable	Off Therapy	First on Therapy	Last on Therapy	p Value		
				1*	2†	3‡
Dosage (mg)	0	191 ± 59	280 ± 81	—	0.0007	—
Maximum heart rate (beats/min)	154 ± 17	133 ± 13	134 ± 14	0.00001	0.9	0.0003
Maximum heart rate predicted by age (mean percentage)	80 ± 8	69 ± 6	73 ± 5	0.00002	0.01	0.002
Maximum workload (W)	140 ± 58	134 ± 55	137 ± 58	0.9	0.6	0.4
Heart rate threshold of arrhythmias (beats/min)	132 ± 13	125 ± 9	125 ± 14	0.03	0.7	0.1
Workload at arrhythmia onset (W)	111 ± 42	120 ± 45	108 ± 41	0.08	0.7	0.5
Heart rate at arrhythmia disappearance (beats/min)	143 ± 17	131 ± 13	128 ± 16	0.004	0.4	0.02
Onset of ventricular bigeminy (beats/min)	144 ± 15	133 ± 10	125 ± 9	0.002	0.05	0.005
Patients with ventricular bigeminy (%)	15 (75%)	11 (55%)	8 (40%)	0.2	0.3	0.03
Patients without arrhythmias (%)	0 (0%)	3 (15%)	4 (20%)	0.08	0.7	0.04
Patients with ventricular couplets (%)	14 (70%)	4 (20%)	1 (5%)	0.003	0.1	0.0001
Patients with nonsustained ventricular tachycardia (%)	7 (35%)	0 (0%)	0 (0%)	0.006	1	0.006
Patients with polymorphic arrhythmias (%)	17 (85%)	6 (30%)	6 (30%)	0.001	1	0.001
Patients with prevalent left bundle branch block morphology (%) <sup>§</sup>	10 (50%)	13 (65%)	12 (60%)	0.3	0.7	0.5
Patients with prevalent right bundle branch block morphology (%) <sup>§</sup>	7 (35%)	3 (15%)	3 (15%)	0.1	1	0.1

\* First test off therapy versus first test on therapy.

† First test on therapy versus last test on therapy.

‡ First test off therapy versus last test on therapy.

§ For morphologies of ventricular arrhythmias, during the first exercise test 3 patients presented polymorphic arrhythmias but it was not possible to discriminate a prevalent morphology, whereas during the 2 exercise tests on therapy it was not possible to discriminate a prevalent morphology in 1 subject.

signal-averaged electrocardiography, and echocardiography with Doppler study.

The cycling exercise test was done using a 25-W × 2 protocol that assessed the first exercise tests performed off and on  $\beta$  blocker (within 1 month) and the last test performed on  $\beta$  blocker. Acebutolol, a  $\beta$  blocker with intrinsic sympathicomimetic activity, was chosen because it was used since the beginning in all patients, produces less arterial hypotension, and because of the good results on VAs was continued throughout the follow-up. All exercise tests were performed until onset of muscular fatigue or appearance of VT. Maximum heart rates (HRs) and workloads were recorded. The following features of VAs were analyzed: HR and workload at onset of VAs; most frequent ventricular premature beat (VPB) morphologies; episodes of ventricular bigeminy, ventricular couplets, VT, and corresponding HR; and behavior of VAs after stopping exercise. During the first exercise test off  $\beta$  blocker we also considered the mode of onset of VAs (coupling interval and morphology of the first VPB and corrected QT interval of the last sinus beat preceding onset of arrhythmia). Features of VAs under maximum exercising workload were recorded.

All continuous variables were expressed as mean  $\pm$  SD. Student's paired and unpaired *t* tests were used to compare normally distributed data and Kruskal–Wallis test was used in all other cases. Chi-square test was used to compare noncontinuous variables expressed as proportions.

## Results

Twenty patients (8 men, 12 women) were analyzed. Their age at the time of baseline exercise tests was  $27 \pm 13$  years and their age at the last test was  $38 \pm 13$  years, so the mean follow-up was  $11 \pm 8$  years (range 2 to 27).

Electrocardiography performed in the absence of therapy was considered normal in all patients. Sinus bradycardia at rest was found in 30%. Corrected QT interval was normal (mean  $415 \pm 24$  ms). During follow-up 1 patient had a first-degree atrioventricular block and 1 a relatively short QT interval. Sinus bradycardia was recorded in another 2 patients. Follow-up electrocardiograms did not differ significantly from baseline in the remaining patients. On signal-averaged electrocardiogram late potentials were present in 4 subjects (20%) at the first assessment and at last follow-up.

Two-dimensional echocardiogram detected mild right ventricular dilation in 5 patients (25%) and 2 of them also had mild left ventricular dilation. One patient had right ventricular wall motion abnormalities (akinesia of the subtricuspid region and basal free wall). These findings did not change significantly during follow-up. None of the patients fulfilled the criteria for a definite diagnosis of arrhythmogenic right ventricular cardiomyopathy.<sup>24</sup>

For exercise testing off therapy the initiation, progression, and termination of VAs were studied (Table 1). Patients reached a maximum HR of  $154 \pm 17$  beats/min (equivalent of  $80 \pm 8\%$  of maximum HR predicted for age) and a maximum workload of  $140 \pm 58$  W. Mean HR at onset of the first VPB was  $132 \pm 13$  beats/min (minimum 115 beats/min, maximum 156 beats/min) under a mean workload of  $111 \pm 42$  W. The coupling interval of the first VPB was  $407 \pm 30$  ms. The corrected QT interval of the preceding sinus beat was  $424 \pm 22$  ms. The first VPB revealed left bundle branch block or right bundle branch block morphology. VPBs with left bundle branch block morphology showed an inferior-axis deviation ( $75^\circ$  to  $105^\circ$ ) in 7 subjects and left-axis deviation ( $\leq -30^\circ$ ) in 3 subjects.

VPBs with right bundle branch block morphology showed left- or right-axis deviation in 9 subjects and a normal axis in 1. In 16 patients (80%) VAs began as monomorphic and became polymorphic as exercise progressed. In 3 patients (15%) VAs remained monomorphic during the entire exercise test. Ventricular bigeminy occurred in 75%, appearing at a mean HR of  $144 \pm 15$  beats/min (minimum 130 beats/min, maximum 175 beats/min). Predominantly polymorphic ventricular couplets occurred in 70%, appearing at a mean HR of  $145 \pm 15$  beats/min (minimum 125 beats/min, maximum 176 beats/min) and a workload of  $129 \pm 51$  W. Polymorphic nonsustained VT was detected in 7 subjects (35%), occurring at a mean HR of  $158 \pm 16$  beats/min (minimum 140 beats/min, maximum 175 beats/min) with a maximum ventricular rate of  $191 \pm 28$  beats/min. Two subjects with nonsustained VT were index cases, and 5 were found during cascade screening and had the N2386I mutation. Under maximum workload the most severe VAs observed were nonsustained VTs in 35% and couplets in 30%, whereas single VPBs were detected in the remaining subjects. Overall, the most common VPB morphologies seen during exercise testing were characterized in 50% by left bundle branch block (35% with inferior-axis deviation, 15% with left-axis deviation) and in 35% by right bundle branch block (with variable-axis deviation), whereas the 2 morphologies were equally distributed in 15%. Stopping exercise led to the disappearance of VAs in all subjects immediately after or within the first minute of resting. Mean HR when the VAs disappeared differed significantly from the mean HR threshold ( $p = 0.03$ ).

For baseline exercise testing on  $\beta$ -blocker therapy VAs disappeared completely in 15% of patients, nonsustained VTs disappeared, and couplets persisted in 20%. Therapy was effective in converting polymorphic to monomorphic patterns in 11 patients (55%). Maximum HR was decreased significantly compared to the test off  $\beta$  blocker, whereas mean maximum workload did not change significantly. Arrhythmias developed at a lower HR threshold than in the test off therapy ( $p = 0.03$ ).

For exercise testing on therapy at the last follow-up,  $\beta$ -blocker dosage titration was needed in 10 patients. No significant differences emerged compared to results of the 2 exercise tests conducted on therapy (Table 1). Nonsustained VTs did not reappear, ventricular couplets decreased from 20% to 5%, and polymorphic patterns persisted in 30%. Comparing the first exercise test off therapy to the last on therapy, 14 patients (70%) responded to therapy. In detail, in 7 patients with nonsustained VT as the most severe arrhythmia, this arrhythmia disappeared ( $p = 0.006$ ); in 7 patients with couplets as the most severe arrhythmia, this arrhythmia disappeared ( $p = 0.006$ ); and in 6 patients with single VPBs, VPBs persisted throughout follow-up. During the last exercise test VPBs of left bundle branch block morphology persisted compared to right bundle branch block (60% vs 15%,  $p = 0.006$ ). VPBs with left bundle branch block morphology presented inferior-axis deviation (45%) or left-axis deviation (15%). Mean HR threshold of the VAs decreased but not significantly and workload remained unchanged.

During follow-up only 2 patients became symptomatic. A 52-year-old woman had an implantable cardioverter-

defibrillator because of an episode of syncope. A calcium channel blocker was added to  $\beta$ -blocker therapy. No further implantable cardioverter-defibrillator events or episodes of syncope were recorded during a 4-year follow-up. A 20-year-old woman developed syncope while dancing. Beta-blocker therapy was increased and no nonsustained VT appeared. Importantly, silent carriers were treated with  $\beta$  blocker and no VAs were recorded during follow-up.

## Discussion

RyR2 mutation carriers frequently have a family history of sudden death or they may present with effort-induced syncope or palpitations. Electrocardiogram is usually normal and late potentials may be present only in a minority of cases.<sup>17-19</sup> Imaging techniques in most cases reveal normal findings.<sup>2,20</sup> Exercise testing and Holter monitoring may often reveal VAs.<sup>22,25</sup> Exercise testing is indicated for assessing subjects with known or suspected effort-induced VAs and ascertaining the efficacy of medical therapy. Antiarrhythmic strategies usually consist of high-dose  $\beta$  blockers; nadolol and propranolol are generally used.<sup>19</sup> The antiarrhythmic effect is caused by an inhibition of the sympathetic action to  $\beta$  receptors and it may also improve RyR2 function by restoring the balance between phosphorylation and dephosphorylation and attenuate the increase of sarcoplasmic reticulum calcium content.<sup>2,4,5</sup> Beta-blocker therapy is associated with lower event rates but usually fails to completely suppress VAs. Further studies on concomitant therapies (verapamil, flecainide, implantable cardioverter-defibrillator, left ventricular sympathetic denervation) are ongoing.<sup>26-29</sup>

In this study acebutolol was used; thus it contributes to further information on therapy for RyR2 mutation carriers. Furthermore, detailed analysis of arrhythmic patterns with and without therapy was assessed. Analysis of the first exercise test off therapy provided interesting information on features of the VA pattern. VAs occurred when a mean HR of  $132 \pm 13$  beats/min and a workload of  $111 \pm 42$  W were reached (Table 1). The first VPB did not show particular electrocardiographic characteristics. In most patients VAs appeared with a monomorphic pattern that became polymorphic as they continued to exercise. Ventricular bigeminy was common. With the increase of HR there was an exacerbation of VAs; couplets ( $145 \pm 15$  beats/min,  $p = 0.05$ ) and nonsustained VTs ( $158 \pm 16$  beats/min,  $p = 0.000\ 01$ ) appeared at a higher HR compared to onset of VAs. The low frequency of VT observed could be explained by the fact that only few patients exceeded their submaximal HR and only 2 patients were index cases. Moreover, phenotypic manifestations may be variable.<sup>20,22</sup> All patients' VAs disappeared immediately or shortly after they stopped exercising, implicating the importance of the vagal reactivation.

The first exercise test on  $\beta$  blocker showed that the mean HR threshold of VAs decreased significantly ( $p = 0.03$ ). A similar result was found at the end of follow-up by Haugaa et al<sup>30</sup> using different  $\beta$  blockers. During the last exercise test the HR threshold decreased but not in a significant manner and importantly it was not accompanied by an increase of VA severity. Therapy with  $\beta$  blocker was able to

decrease the maximum HR significantly, reaching the same level of workload as off therapy, thus not permitting more complex VAs to develop. Overall, in 20% VAs disappeared ( $p = 0.04$ ). In 3 patients the decrease in maximum HR below the personal threshold of VAs could explain why no VAs occurred. The observation that further titration led to a decrease of VAs in only 1 more patient could be explained by the fact that maximum HR did not change significantly, probably because of intrinsic sympathicomimetic activity. In addition,  $\beta$  blocker was efficient in decreasing the complexity of the arrhythmic pattern in most patients, inhibiting the development of nonsustained VT, decreasing couplets significantly (to 5%), and decreasing polymorphic patterns (to 25%). Previous observations support the hypothesis that the  $\beta$ -blocker effect is caused by a decrease of maximum HR and additional mechanisms involved in the decrease of VAs.<sup>2,4,5</sup>

It is important to emphasize that 3 patients (15%) only had single monomorphic VPBs that remained monomorphic in 2 throughout follow-up. The prompt initiation of therapy does not permit us to predict if more complex arrhythmias could appear later in the absence of therapy. In these subjects the first exercise test alone could not distinguish idiopathic adrenergic VAs from those linked to RyR2 mutations because the latter were identified by family screening. Diagnosis was achieved by analyzing the family history of sudden death, demonstrating effort-induced polymorphic VPBs in other family members, and repeating the exercise test (which revealed a different VPB morphology in 1 subject). Identifying disease-causing RyR2 mutations through genetic screening confirms the diagnosis.

It is important to note that  $\beta$ -blocker therapy was unable to modify the arrhythmic pattern in 30% of patients characterized by single VPBs. Although a different type of  $\beta$  blocker was used in this study, the findings are similar to data published by Haugaa et al<sup>30</sup> who reported no effect of  $\beta$ -blocker therapy in 43% of subjects and that less severe arrhythmias were not decreased despite the maximum tolerated dose of  $\beta$  blocker. The observation that noncomplex VAs persisted throughout follow-up could be interpreted as a protective mechanism of  $\beta$  blockers against more severe arrhythmias. Further studies in larger series are needed to establish whether some  $\beta$  blockers have greater efficacy than others and if their efficacy depends on the specific mutation on the RyR2 gene and severity of the arrhythmic pattern.

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