Calcium channel blockers and beta-blockers versus beta-blockers alone for preventing exercise-induced arrhythmias in catecholaminergic polymorphic ventricular tachycardia

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BACKGROUND The mainstay of therapy for catecholaminergic polymorphic ventricular tachycardia (CPVT) is maximal doses of β-blockers. However, although β-blockers prevent exercise-induced ventricular tachycardia (VT), most patients continue to have ventricular ectopy during exercise, and some studies report high mortality rates despite β-blockade.

OBJECTIVE The purpose of this study was to investigate whether combining a calcium channel blocker with β-blockers would prevent ventricular arrhythmias during exercise better than β-blockers alone since the mutations causing CPVT lead to intracellular calcium overload.

METHODS Five patients with CPVT and one with polymorphic VT (PVT) and hypertrophic cardiomyopathy who had exercise-induced ventricular ectopy despite β-blocker therapy were studied. Symptom-limited exercise was first performed during maximal β-blocker therapy and repeated after addition of oral verapamil.

RESULTS When comparing exercise during β-blockers with exercise during β-blockers + verapamil, exercise-induced arrhythmias were reduced: (1) Three patients had nonsustained VT on β-blockers, and none of them had VT on combination therapy. (2) The number of ventricular ectopics during the whole exercise test went down from 78 ± 59 beats to 6 ± 8 beats; the ratio of ventricular ectopic to sinus beats during the 10-second period recorded at the time of the worst ventricular arrhythmia went down from 0.9 ± 0.4 to 0.2 ± 0.2. One patient with recurrent spontaneous VT leading to multiple shocks from her implanted cardioverter-defibrillator (ICD) despite maximal β-blocker therapy (14 ICD shocks over 6 months while on β-blockers) has remained free of arrhythmias (for 7 months) since the addition of verapamil therapy.

CONCLUSIONS This preliminary evidence suggests that β-blockers and calcium blockers could be better than β-blockers alone for preventing exercise-induced arrhythmias in CPVT.

KEYWORDS Catecholaminergic polymorphic ventricular tachycardia; β-Adrenergic blockers; Calcium channel blockers; Exercise; Ryanodine

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Introduction

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a congenital disease characterized by exercise- or stress-induced syncope or cardiac arrest due to ventricular tachyarrhythmias in the absence of QT prolongation or organic heart disease. The hallmark of this disease is the reproducible provocation of polymorphic ventricular arrhythmias during exercise. Typically, patients with CPVT have a normal electrocardiogram (ECG) at rest; however, as the intensity of exercise increases, they develop atrial tachycardia or fibrillation, unifocal and then multifocal ventricular extrasystoles, a diagnostic bidirectional ventricular tachycardia (VT), and polymorphic VT. Deterioration of exercise-induced polymorphic VT to ventricular fibrillation (VF) has been documented in CPVT.

Ever since the causal association between stress and arrhythmic symptoms of CPVT was recognized, β-blockers have been the mainstay of therapy. Moreover, since polymorphic VT is reproducibly induced with exercise in the majority of patients with CPVT, it is common practice to use repeated exercise testing to evaluate the efficacy of β-blocker therapy. Indeed, β-blockers are very effective for preventing exercise-induced sustained polymorphic VT. However, the majority of patients with CPVT continue to have different degrees of ventricular ectopy during exercise despite maximally tolerated dosages of β-blockers. Moreover, some studies report high mortality rates and a high incidence of recurrent polymorphic VT despite β-blocker therapy. Thus, additional forms of therapy are needed for this potentially lethal disease.
The majority of mutations causing CPVT lead to intracellular calcium overload, we theorized that adding calcium channel blockers to a therapeutic regimen of β-blockers would prevent ventricular arrhythmias better than β-blockers alone.

**Methods**

**Patients**

Seven patients with CPVT were studied. All the CPVT patients have a history (or familial history) of syncope and/or cardiac arrest, and all of them have documented exercise-induced...
polymorphic and/or bidirectional VT. Two of these patients had total suppression of exercise-induced ventricular arrhythmias with β-blockers and were therefore not included in this study. The remaining five patients, who had reproducible provocation of exercise-induced ventricular ectopy despite maximally tolerated doses of β-blocker therapy, were included (Table 1). None of the CPVT patients have been genotyped. However, their clinical history and documented arrhythmias are diagnostic of CPVT (Figure 1A).1,3 We also included a 69-year-old female with exercise-induced atrial and ventricular arrhythmias. The characteristics of the last patient are less typical for CPVT because she is elderly and asymptomatic and because she has left ventricular hypertrophy consistent with hypertrophic cardiomyopathy. She was nevertheless included because she has reproducible provocation of repetitive nonsustained polymorphic VT on submaximal exercise (Figure 2A). It should be noted that even though CPVT was initially considered a disease of children,2 CPVT presenting in adulthood has recently been described.7 Also, although CPVT is considered a channelopathy causing electrical but no morphologic abnormalities, in an animal model of CPVT, mice with calsequestrin 2 mutations developed hypertrophic cardiomyopathy as a late manifestation.9

Exercise testing

To establish the diagnosis of CPVT and confirm the reproducibility of exercise-induced arrhythmias, symptom-limited exercise tests were performed twice (10 minutes apart) in the absence of therapy. Oral β-blockers were started and gradually increased until side effects (fatigue) occurred. The doses were then reduced to the maximally tolerated dosages, and a maximal exercise stress test was performed. To confirm the reproducibility of exercise-induced arrhythmias despite β-blockers, a second exercise test was performed after 10 minutes of rest. As mentioned above, only the six patients who had reproducible provocation of ventricular arrhythmias with exercise despite adequate β-blocker therapy were included in this study. These six patients then received oral verapamil (at daily doses of 2–3 mg/kg/day for children and 240 mg/day for adults) in addition to their permanent β-blocker regimen, and a symptom-limited exercise test was repeated 1–2 weeks later. To test for the reproducibility of efficacy of this combination therapy, a similar test was performed after 10 minutes of rest. One patient (patient 5) with typical CPVT refused to repeat the exercise stress test after initiation of the combination therapy because of intense fear of exercise-induced arrhythmias. She was never-

Figure 2  Asymptomatic 69-year-old female (patient 5) with reproducible provocation of exercise-induced polymorphic VT. A: The baseline ECG is strictly normal; the QTc is 410 ms. B: During exercise in the absence of drugs she develops incessant nonsustained polymorphic VT with only isolated sinus complexes. C: During therapy with atenolol 150 mg/day, she no longer has VT but has ventricular couplets, and ventricular triplets (*). During therapy with atenolol 150 mg + verapamil 240 mg/day, she has only isolated ventricular ectopy during maximal exercise.
the McNemar test was used.

Wilcoxon signed ranks test, while for dichotomous variables, the comparison was done using the paired t-test. For continuous variables and as number and percent of dichotomous variables, all statistical analyses were nonparametric. For continuous variables, the measured outcome was the degree of exercise-induced arrhythmias, expressed as (1) the presence or absence of atrial fibrillation or nonsustained VT; (2) the total number of ventricular ectopic beats during the whole exercise test; and (3) the number of ventricular ectopic beats during the worst 10-second period of the exercise test. Data are presented as number ± standard deviation for all continuous variables and as number and percent of dichotomous variables. Because of the very small number of individuals, all statistical analyses were nonparametric. For continuous variables, the comparison was done using the paired Wilcoxon signed ranks test, while for dichotomous variables the McNemar test was used. P < .05 (two tailed) was considered statistically significant. The SPSS statistical package was used to perform all statistical evaluation (SSPS Inc., Chicago).

Results
Patient characteristics
The six patients included in the study are from four different families (Table 1). Before the onset of β-blocker therapy, one of them had cardiac arrest, two had near drowning, and two had recurrent malignant syncope with seizures. Three of these patients also experienced arrhythmic symptoms while receiving β-blocker therapy (recurrent syncope in two patients and multiple ICD shocks for polymorphic VT in one patient). The other three patients were rendered asymptomatic by β-blockers but had persistent and reproducible exercise-induced ventricular arrhythmias despite β-blockade.

Effects of combined (calcium- and β-blocker) therapy on exercise testing
The addition of verapamil to the β-blocker regimen did not significantly affect the sinus rate recorded at baseline or at the onset of ventricular arrhythmias (Table 2). However, all patients had fewer exercise-induced ventricular arrhythmias dur-

<table>
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<th>Table 2</th>
<th>Exercise testing of patients with CPVT*</th>
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<tr>
<td>Variable</td>
<td>β-blockers</td>
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<tr>
<td>Sinus rate at baseline, bpm</td>
<td>64 ± 9</td>
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<tr>
<td>Sinus rate at the onset of ventricular arrhythmias, bpm</td>
<td>117 ± 19</td>
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<td>Sinus rate at the time of the worst arrhythmias, bpm</td>
<td>135 ± 29</td>
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<td>Sinus rate at maximal exercise, bpm</td>
<td>150 ± 22</td>
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<tr>
<td>Maximal treadmill speed,† km/hour</td>
<td>6.9 ± 1.3</td>
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<tr>
<td>Maximal treadmill grade‡</td>
<td>10.8° ± 6.1°</td>
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<tr>
<td>Maximal number of ventricular ectopic beats</td>
<td>78 ± 59</td>
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<td>Maximal number of ventricular ectopic beats during the worst 10 seconds period</td>
<td>11.0 ± 3.1</td>
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<tr>
<td>Maximal ratio of ventricular ectopic to sinus beats during the worst 10-second period‡</td>
<td>0.9 ± 0.4</td>
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*Data for five patients. All exercise tests were symptom limited (the only reason for discontinuation was patient exhaustion). †Maximal treadmill speed and grade sustained for at least 1 minute. ‡To obtain this value, the number of ventricular ectopics was divided by the number of sinus beats recorded during a 10-second period at the time of the worst ventricular arrhythmia.
ing calcium- and β-blocker therapy than during β-blocker therapy alone (Figures 1–3). Figure 3A shows the total number of ectopic beats recorded for each patient during four exercise tests (the first two tests on β-blockers and the second pair during therapy with β-blockers and verapamil). All four tests were symptom limited, and the only reason for discontinuation was patient exhaustion. The second test on β-blockers alone already shows fewer ectopic beats in comparison with the first test (Figure 3A), which reflects the fact that the rest period between the first two tests was brief, resulting in earlier exhaustion during the second test on β-blockers. Nevertheless, a further unequivocal and obvious decrement in the amount of ectopy occurred after 1–2 weeks of therapy with β-blockers plus calcium blockers. Importantly, the maximal treadmill speed and treadmill grade (reflecting the maximal exercise challenge) during exercise tests number 1 and 3 (the first exercise test performed on β-blockers and the first exercise test on combination therapy, respectively) were similar (Table 2). Figure 3B shows the ratio of ectopic beats to sinus beats during a 10-second period at the time of the worst ventricular arrhythmia recorded during each of the four tests. Again, the improvement in the degree of ventricular arrhythmias achieved after the addition of verapamil is unequivocal for each patient. Finally, exercise-induced nonsustained VT was recorded during β-blocker therapy in four patients but never during combined therapy. Exercise-induced atrial tachycardia/fibrillation occurred in the absence of therapy in two patients, during β-blockers in one, and during combined therapy in none.

Effects of combined (calcium- and β-blocker) therapy on clinical outcome

The three patients who were asymptomatic on β-blocker therapy have remained free of clinical arrhythmias while on combined therapy for 13 ± 8 additional months. Two patients who had recurrent syncope while on β-blockers had a single episode of syncope while receiving combination therapy. This includes patient 1 and her 8-year-old son, who had a seizure episode triggered by panic. Of note, the child had a totally negative exercise test on combination therapy (respectively) during exercise tests number 1 and 3 (the first exercise test performed on β-blockers and the first exercise test on combination therapy, respectively) were similar (Table 2). Figure 3B shows the ratio of ectopic beats to sinus beats during a 10-second period at the time of the worst ventricular arrhythmia recorded during each of the four tests. Again, the improvement in the degree of ventricular arrhythmias achieved after the addition of verapamil is unequivocal for each patient. Finally, exercise-induced nonsustained VT was recorded during β-blocker therapy in four patients but never during combined therapy. Exercise-induced atrial tachycardia/fibrillation occurred in the absence of therapy in two patients, during β-blockers in one, and during combined therapy in none.

Side effects

Four patients intermittently complained of fatigue while on β-blocker therapy, but this symptom did not worsen after the addition of verapamil. One mother and her son suffer from chronic photophobia (requiring constant use of sunglasses) ever since verapamil therapy was started.

Discussion

CPVT is a rare disease, and spontaneous arrhythmias occur sporadically yet may be fatal. Therefore, demonstrating clinical efficacy for any drug therapy is difficult. On the other hand, most patients with CPVT (and all the patients ultimately included in this study) have easy and reproducible provocation of arrhythmias with exercise. For the present study, we took advantage of the easy provocation of arrhythmias in CPVT and showed that adding a calcium channel blocker to a β-blocker regimen further reduces the severity of exercise-induced arrhythmias.

Main findings

Clinical efficacy of the verapamil plus β-blocker combination was clearly demonstrated for one patient, who had a dramatic reduction in the number of spontaneous VT events triggering ICD shocks. For the other patients, prevention of exercise-induced VT and/or obvious reduction of exercise-induced ectopy were demonstrated. Arrhythmia suppression by the verapamil + β-blocker combination occurred without affecting the sinus rate recorded at the time of ventricular arrhythmias. This suggests that verapamil reduced the amplitude of delayed depolarizations (DADs) below the amplitude threshold required for triggering ventricular arrhythmias (see below).

Rationale for combining calcium and β-blockers

Normally, small calcium currents that enter the cardiomyocyte through L-type calcium channels in the cell membrane trigger a larger flow of calcium current (needed for the excitation-contraction coupling in the heart) from intracellular deposits (the sarcoplasmic reticulum). During stress, stimulation of β-adrenergic receptors results in cyclic-AMP-dependent phosphorylation of the ryanodine channels, opening these channels to boost the flow of calcium from the sarcoplasmic reticulum. In CPVT, mutations in the genes encoding for the ryanodine channel or the calcium-buffering protein calsequestrin (the calcium-binding protein that controls its release through the ryanodine channel) lead to excessive release of calcium currents. This excess of positive ion calcium current depolarizes the myocyte at the end of the action potential, creating DADs. As beautifully explained by other investigators, calcium-mediated DADs reaching threshold potential trigger the arrhythmias of CPVT. Thus, patients with CPVT need β-blockers to prevent the adrenergic augmentation of calcium flow through the genetically defective ryanodine channel. Verapamil could further prevent arrhythmias by blocking the L-type calcium channels in the cell membrane, reducing the amount of intracellular calcium that incites the calcium-dependent calcium release from the defective sarcoplasmic reticulum. Verapamil could further reduce the passage of calcium through the ryanodine channel either through a direct blocking action or by further reducing cyclic AMP. In addition, the negative dromotropic effects of verapamil may be important because patients with CPVT often have catecholaminergic atrial fibrillation. By further decreasing the ventricular rate during atrial fibrillation, verapamil may prevent rate-dependent triggered (DAD mediated) ventricular arrhythmias. Finally, in animal models of CPVT, DADs generated in the epicardium are more likely to trigger extrasystoles. This could be related to a larger influx of calcium through L-type calcium channels in epicardial cells. Block-
ing epicardial DADs with verapamil is particularly important because extrasystoles originating in the epicardium increase the dispersion of repolarization and facilitate the degeneration of bidirectional VT to VF. Thus, at least in theory, patients with CPVT should receive both β-blockers and calcium blockers to prevent the onset of VT (β-blockers) and its degeneration to VF (calcium blockers).

**Previous studies**

A single case of bidirectional VT due to Andersen’s syndrome (a rare disease caused by malfunction of the inward-rectifier potassium channel) that responded to therapy with verapamil was reported by Kannankeril et al. More recently, Swan et al demonstrated that a single dose of intravenous verapamil to six patients with CPVT, including five patients receiving oral β-blocker therapy, significantly reduced the amount of exercise-induced VT in an acute study.

**Limitations**

Because of the small number of patients and the limited follow-up, our results should be viewed as preliminary. Also, the fact that one patient had syncope during panic, while receiving therapy that was protective during exercise, emphasizes that emotional and physical stress cannot always be equated. Thus, negative exercise tests do not invariably imply an event-free prognosis.

**Clinical implications**

CPVT is a malignant disease. Without therapy, 30%–50% of patients die suddenly at a young age. Even with β-blocker therapy, unacceptably high mortality rates—as high as 19%—have been reported. Therefore, some investigators have proposed ICD implantation for high-risk patients. However, ICD implantation in CPVT has drawbacks: (1) CPVT mostly affects children, and ICD implantation in children incurs significant morbidity and complications. (2) (Poly) ventricular VT will not terminate with ICD shocks. Programming the ICD with long detection times so shocks are delivered after this VT (triggered activity) degenerates to VF (reentry) is problematic. (3) ICD shocks are painful and frightening, and the resulting catecholamine surge would be extremely proarrhythmic in CPVT. Fatal arrhythmic storms triggered by ICD shocks may occur, and frequent shocks may be emotionally devastating for children. Therefore, therapy aimed at preventing the onset of VT should be optimized. β-blocker therapy is mandatory, but it is not always effective. Verapamil (in addition to β-blockers) may further reduce the amount of exercise-induced arrhythmias and should be strongly considered for patients with persistent symptoms. We do recognize that the data presented here are very limited and should be viewed as preliminary. Nevertheless, considering the theoretical rationale for this therapy and recognizing that standard therapy is far from ideal, we would argue that prescribing β- and calcium blockers to all patients with CPVT who have exercise-induced arrhythmias despite adequate β-blockade is a reasonable approach.

**References**


