Pretreatment with Atropine to Reduce Exercise-triggered Ventricular Ectopy in Patients with Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

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1.0 Background

Catacholaminergic Polymorphic Ventricular Tachycardia (CPVT) is an inherited arrhythmia syndrome characterized by exercise-induced ventricular arrhythmias in patients with structurally normal hearts. It is associated with a high rate of sudden cardiac death in affected patients and has a prevalence in the general population of ~1:10,000. It is caused by dysregulated intracellular calcium handling due to mutations in the gene encoding the sarcoplasmic reticulum (SR) calcium release channel (RyR2) or RyR2-binding proteins (Casq2, triadin, calmodulin). Exercise causes ventricular ectopy by exacerbating SR dysfunction due to enhanced calcium uptake from beta-adrenergic stimulation and therefore enhanced Ca leak via the RyR2 channels. Diastolic calcium leak causes delayed after depolarizations (DADs), which are a common mechanism for fatal ventricular arrhythmias.

2.0 Rationale and Specific Aims

First line therapy for CPVT is beta-blockade which is effective in many patients. Beta-blockade acts to suppress exercise-induced ectopy. However, many patients are incompletely suppressed with beta-blockade and undergo treatment with second-line therapies such as flecainide. Patients who have breakthrough arrhythmias on beta-blocker therapy may also undergo placement of an implantable cardioverter defibrillator (ICD), but ICD's do not provide complete protection against sudden cardiac death in CPVT patients due to the potential for fatal ICD storm (repeated ICDs shocks due to recurrent ventricular arrhythmias). Taken together, current therapies for CPVT are not completely effective for many affected patients and the development of alternative approaches to reducing sudden cardiac death is needed.

Recently, experimental evidence from mouse models of CPVT have demonstrated that mutations causing RyR2 dysfunction also promote sinus node dysfunction in the form of resting sinus bradycardia and/or chronotropic incompetence (an inappropriately slow sinus node rate during peak exercise). This finding is supported by observations in patients with CPVT. While it may seem that a slow heart rate would be protective for patients with CPVT because they have an exercise-induced arrhythmia, we present evidence below (section 3.0) from mouse models and human observations to support the idea that a slow sinus node rate during exercise (when catecholamine levels are high) creates an unfavorably long diastolic interval that promotes occurrence of DADs. By increasing the sinus node rate during exercise, the diastolic interval can be shortened which has been found to reduce the occurrence of DADs (and ventricular ectopy) in mice. Therefore, we aim to test the following hypothesis in humans:

Specific Aim: **To test the hypothesis that increasing the sinus node rate with atropine treatment prior to exercise will reduce exercise-triggered ventricular ectopy compared to baseline in patients with CPVT.**

3.0 Animal Studies and Previous Human Studies

Three studies by Kannankeril et al published in the early 2000s demonstrated that the parasympathetic nervous system exhibits demonstrable effects on cardiac electrophysiology during rest, exercise, and recovery. In the first group, parasympathetic tone was evaluated during peak exercise and recovery. 10 subjects with normal cardiac function were asked to exercise on a recumbent bike in two sessions separated by 24 hours. During the second session, subjects received atropine prior to exercise. Through serial BP, HR, and EKGs, the researchers showed a significant parasympathetic effect on cardiac electrophysiology is present throughout rest, peak exercise (although decreased), and recovery. In the second study, researchers evaluated parasympathetic effects on cardiac electrophysiology during rest, exercise, and recovery using NIPS and atropine in 9 subjects with normal LV function, intact SA or AV node (preferably both), and a dual chamber device (ICD or PM). Through a series of four sessions, a significant parasympathetic effect on sinus cycle

length and AV block cycle length during rest, exercise, and recovery was revealed. Importantly, they noted that parasympathetic effect is greatest at rest, smallest during exercise, and intermediate during recovery. In the third study, parasympathetic effects were evaluated in 5 patients with LV dysfunction (EF 30-40%) and dual chamber devices (ICD or PM) capable of NIPS. The study design was similar to the second, and the results showed that parasympathetic effects on sinus cycle length and AV block are measurable during exercise and recovery. Heart disease and ventricular dysfunction decreased the parasympathetic effect on ventricular refractoriness during exercise and recovery compared to normal controls. Thus, it was concluded that parasympathetic tone does persist through exercise and recovery, and diminished parasympathetic effect on ventricular refractoriness during exercise and recovery may be responsible for the increased risk of sudden death noted during exercise and recovery. [1,2]

More recent studies by Faggioni et al. suggest that decreased parasympathetic tone and accelerated sinus rhythm may prevent CPVT in both mice and patients. In order to test the hypothesis that CPVT is suppressed by supraventricular overdrive stimulation, in a randomized crossover design, two CPVT mouse models (Casq2-/- and $RyR2^{R4496}$ +/-) underwent pretreatment with either distilled water or atropine prior to catecholamine challenge with isoproterenol. Of the Casq2 -/- mice, 86% had significantly reduced ventricular arrhythmia when treated with atropine vs treatment with distilled water prior to ISO. The hypothesis was again tested using atrial overdrive pacing instead of atropine during catecholamine challenge (ISO for Casq2 -/- mice, ISO + caffeine in $RyR2^{R4496}$ +/-mice).The atrial pacing was set to match the peak sinus rate with catecholamine challenge alone. Atrial overdrive pacing completely prevented ventricular arrhythmia in 84% of Casq2 -/- mice and 88% of $RyR2^{R4496}$ +/- mice during catecholamine challenge with ventricular premature beats significantly reduced in both. In single myocyte studies, ventricular myocytes isolated from Casq2 -/- mice were loaded with FURa-2 AM for intracellular calcium measurements. Myocytes were then stimulated at increasing pacing rates after addin ISO. Higher pacing frequencies reduced the diastolic interval and progressively reduced the incidence of SCWs. [3]

Finally, a CPVT registry of patients with RyR2 mutation was screened for antiarrhythmic-naïve individuals who underwent exercise stress testing. Of the 42 drug-naïve patients with ventricular arrhythmia on exercise testing, 18 patients reached 85% of maximum predicted HR during exercise testing and exercised beyond onset of ventricular arrhythmia. These patients were included in the study. All 18 patients in the analysis developed ventricular arrhythmia by a heart rate 87% of maximum predicted heart rate. In 6 of the 18 patients, ventricular arrhythmia subsided as the sinus HR reached 89-99% of maximum predicted HR. This suggests that in a portion of CPVT patients, ventricular arrhythmia is suppressed with increasing sinus tachycardia. These studies suggest that in patients with CPVT, ventricular arrhythmia may be paradoxically suppressed by atrial tachycardia. [3,4]

1. Kannankeril PJ, Goldberger JJ Parasympathetic effects on Human Cardiac Electrophysiology During Exercise and Recovery. Am J Physiol Heart Circ Physiol. 2002; 282(6):H2091-H2098
2. Kannankeril PJ, Le FK, Kadish AH, Goldberger JJ. Parasympathetic Effects on Heart Rate Recovery after Exercise. J Investig Med. 2004;52(6):394-401
3. Faggioni M, Hwang HS, van der Werf C, et al. Accelerated Sinus Rhythm Prevents Catecholaminergic Polymorphic Ventricular Tachycardia in Mice and in Patients. Circ. Res 2013; 112:689-697
4. Faggioni M, van der Werf C, Knollmann BC. Sinus node dysfunction in catecholaminergic polymorphic ventricular tachycardia: Risk factor and potential therapeutic target? Trends Cardiovas Med. 2014;24:273-278

4.0 Inclusion/Exclusion Criteria

INCLUSION	EXCLUSION
Age ≥ 6 years	Contraindication to treadmill stress testing according to Vanderbilt University Medical Center's clinical protocols (unstable angina, decompensated congestive heart failure, severe hypertension (≥ 170/90 mmHg), acute myocardial infarction (<4 days), moderate to severe aortic stenosis, acute pulmonary embolism, severe pulmonary hypertension, outflow tract obstruction, hypertrophic cardiomyopathy, left main coronary stenosis, left bundle branch block)
Able to provide written informed/consent	Females who are pregnant
Clinical diagnosis of Catacholaminergic Polymorphic Ventricular Tachycardia	In the judgement of the investigator, any clinically significant ongoing medical or surgical condition that might jeopardize the subject's safety or interfere with the conduct of the study
Able to exercise on a treadmill	

5.0 Enrollment/Randomization

For feasibility considerations, this pilot study will be non-randomized. Reasons include: i.) administration of atropine before the first exercise portion would require a 2-day protocol for complete drug-washout; ii) administration of atropine results in symptomatic palpitations and in prior studies increases the rate of voluntary participant withdrawal.

6.0 Study Procedures

General Approach: This is a prospective cross-over trial that will enroll eligible patients with CPVT and perform a baseline treadmill exercise tolerance test (ETT) followed by a repeat treadmill ETT with I.V. atropine administered immediately prior to exercise. Atropine is a parasympathetic blocker and results in sinus tachycardia, which is expected to reduce the diastolic interval thereby reducing delayed after depolarizations and ventricular ectopy compared to baseline. Both ETTs will be performed on the same day with two hours of rest scheduled between ETTs. The primary analysis will be a paired comparison of the number of ventricular ectopic beats recorded during exercise (and recovery) at baseline and following pre-treatment with atropine. Secondary endpoints will include the presence of ventricular ectopy (yes/no), complex ventricular ectopy (couplets or greater, yes/no), and the number of runs of complex ventricular ectopy.

Prior to Enrollment	Patient recruited in clinic or by phone
	Patient will continue all outpatient medications prior to study. Specifically, beta-blocker therapy will <u>not</u> be stopped for this study.
Day 1	
8:00 AM	Arrive to Clinical Research Center (CRC)
	Sign consent forms
8:15 AM	Place peripheral I.V.

8:30 AM	Interrogate Device (ICD) (if ICD present)
	Reprogram therapy detection zones if needed
8:45 AM	Place electrodes for ETT
Part 1	**Baseline Exercise Tolerance Test (ETT)**
	Blood pressure, 12-lead ECG
8:50 AM	Start Treadmill ETT (Standard Bruce Protocol, max time=21 minutes)
	Stage 1 (1.7 mph, 10% grade, 3 mins)
8:53 AM	(if necessary) Begin Stage 2 (2.5 mph, 12% grade, 3 mins)
8:56 AM	(if necessary) Begin Stage 3 (3.4 mph, 14% grade, 3 mins)
8:59 AM	(if necessary) Begin Stage 4 (4.2 mph, 16% grade, 3 mins)
9:02 AM	(if necessary) Begin Stage 5 (5.0 mph, 18% grade, 3 mins)
9:05 AM	(if necessary) Begin Stage 6 (5.5 mph, 20% grade, 3 mins)
9:08 AM	(if necessary) Begin Stage 7 (6.0 mph, 22% grade, 3 mins)
+0:20 mins	Monitored rest recovery period
+2:00 hours	Unmonitored rest period. Patient remains on the CRC
Part 2	**Atropine Pre-treatment Treadmill Exercise Tolerance Test**
11:00 AM	Blood pressure, 12-lead ECG
11:05 AM	Give Atropine (0.04 mg/kg up to max of 3 mg I.V.)
	Start ETT (Standard Bruce Protocol, max time=21 minutes)
	Stage 1 (1.7 mph, 10% grade, 3 mins)
11:08 AM	(if necessary) Begin Stage 2 (2.5 mph, 12% grade, 3 mins)
11:11 AM	(if necessary) Begin Stage 3 (3.4 mph, 14% grade, 3 mins)
11:14 AM	(if necessary) Begin Stage 4 (4.2 mph, 16% grade, 3 mins)
11:17 AM	(if necessary) Begin Stage 5 (5.0 mph, 18% grade, 3 mins)
11:20 AM	(if necessary) Begin Stage 6 (5.5 mph, 20% grade, 3 mins)
11:23 AM	(if necessary) Begin Stage 7 (6.0 mph, 22% grade, 3 mins)
+0:20 mins	Monitored rest recovery period
End of Study	
+4:00 hours	Discharge home after 4 hours of observation
	Erase arrhythmia counters on device and reprogram any changes made to therapy detection zones
	Disconnect from monitor and remove electrodes
	Remove peripheral I.V.
	Discharged from CRC

Exercise Tolerance Test (ETT)

The ETT protocol is adapted from the clinical protocol used at the Vanderbilt Heart and Vascular Institute. The participant will be asked to not eat or drink for 4 hours prior to each session, except for a small amount of water used to take necessary meds. He/she will be instructed to take all medication as prescribed prior to the test. Participants will be instructed to wear clothing and shoes appropriate for exercising on a treadmill. An IV will be placed in order to deliver medication during the testing. For a patient with an ICD, the patient's ICD will be interrogated, and reprogrammed if necessary. Electrodes will be placed for ETT.

The patient will be instructed to stand on the treadmill, and will be asked to begin walking on the treadmill using Bruce protocol. The patient will be encouraged to maintain a minimum heart rate of 85% of his/her age predicted maximum. He/She will be encouraged to walk/run until the end of their comfort zone unless the supervising professional terminates the test before then. The exercise portion of the study is planned to last a maximum of 21 minutes per session. The two sessions will be separated by a 20 minute

supervised rest period followed by a 2 hour unsupervised rest period where the patient will be asked to remain at the CRC. After the second exercise session, a 4+ hour observation period will begin. For a patient with an ICD, any changes to ICD settings will be reprogrammed to previous settings. The patient will be disconnected from monitors and electrodes, and the peripheral IV will be removed. In total, the total time commitment is approximately 8 consecutive hours. The medication used during the testing may cause discomfort or an unpleasant sensation.

Exercise will be terminated prior to the end of the test under the following circumstances:

- Inability to exercise
- Marked exercise-induced hypotension (Decrease in Systolic Blood Pressure >10 mmHg despite increased workload)
- Hypertensive response (Systolic Blood Pressure >230 mmHg and/or Diastolic Blood Pressure > 115 mmHg).
- Sustained ventricular tachycardia
- Development of LBBB or intraventricular conduction delay that cannot be distinguished from ventricular tachycardia
- ST segment depression > 2 mm or ST elevation >1 mm in leads without diagnostic Q waves (except leads V1 or aVR)
- Moderate to severe angina pectoris
- Marked dyspnea or fatigue
- Ataxia, dizziness, or near syncope
- Signs of poor perfusion
- Technical difficulties in monitoring the ECG or systolic blood pressure

At the end of the exercise protocol, the recovery phase will begin. The first phase of recovery is a cool-down phase with the patient walking on the treadmill. The patient will be stopped after 2 minutes, and the patient will be asked to lay supine for the remainder of the recovery period.

Blood pressure, HR, and EKG tracings will be recorded throughout the exercise and recovery period, with patient either walking/running or laying in supine position.

Each patient will be tested individually. There will be no videotaping or audiotaping.

7.0 Risks

The primary endpoint of our study is measurement of ventricular arrhythmias (ectopy). This is an expected outcome of our exercise protocol. Risk of adverse clinical consequences of increased ventricular arrhythmias will be reduced by continuation of the participant's medical therapy of AV nodal blockers (Beta-blockers or calcium channel blockers). Patients with CPVT frequently undergo exercise stress testing as part of routine monitoring. All patients included in our study have successfully completed a minimum of two exercise stress tests with no adverse events. Unexpected findings are cardiac arrest, ICD shock, or death and other unanticipated risks could exist.

Risks associated with Atropine include proarrhythmia, however, based on our preliminary data we expect atropine to reduce ventricular arrhythmias with exercise in patients with CPVT. To manage the risk of proarrhythmia, participants will be observed with continuous cardiac monitoring for 20 minutes following ETT, or until ventricular ectopy has returned to baseline (whichever is longer).

8.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others:

Definitions of adverse events: an adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with the treatment or study protocol.

Adverse events include:

- Worsening (change in nature, severity or frequency) of conditions present at the onset of the trial
- Patient / subject deterioration due to the primary illness
- Intercurrent illnesses
- Drug interactions
- Events related or possibly related to concomitant medications
- Abnormal laboratory values or changes of vital signs, as well as significant shifts from baseline within the range of normal, which the Investigator considers clinically significant.

Unexpected Adverse Drug Reaction: an unexpected Adverse Drug Reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information. Definitions of serious adverse events or serious adverse drug reaction: during clinical investigations, adverse events may occur which, if suspected to be drug-related (adverse drug reactions), must be significant enough to lead to important changes in the way the medicinal product is developed (e.g., change in dose, population, needed monitoring, consent forms). This is particularly true for reactions, which, in their most severe forms, threaten life or function.

A serious adverse event/experience (SAE) or reaction is any untoward medical occurrence that:

1. results in death
2. is life-threatening
3. requires inpatient hospitalization or prolongation of existing hospitalization
4. results in persistent or significant disability/ incapacity (as per reporter's opinion)
5. is a congenital anomaly/birth defect
6. is another medically important condition
7. The term "life-threatening" in the definition of "serious" refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Important medical conditions that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Definition of severity of adverse events:

Mild: Causing no limitation of usual activities; the subject / patient may experience slight discomfort.

Moderate: Causing some limitation of usual activities; the subject / patient may experience annoying discomfort.

Severe: Causing inability to carry out usual activities; the subject / patient may experience intolerable comfort or pain.

Definition of adverse event causality:

The Investigator will determine causality of each adverse event by using the classification criteria: unlikely, likely, or not assessable.

Unlikely: The AE is considered by the Investigator to be due to a pre-existing condition, a known manifestation of the target disease, a recurrent condition, or is likely explained by environmental or diagnostic therapeutic factors or was pre-existing and did not deteriorate.

Likely: The AE occurred during or after administration of the study treatment or a pre-existing event worsened within an appropriate period of time, and at least one of the following criteria is applicable:

- the event could not be explained by the clinical condition or history of the subject, environmental or toxic factors, or other diagnostic or therapeutic measure;
- was an expected ADR associated with study treatment or a class-labeled drug effect;
- AE subsided or disappeared after withdrawal or dose reduction of study treatment; or
- AE recurred after re-exposure to study treatment.

Not assessable: There is insufficient or conflicting evidence for classifying the causality of the AE as likely or unlikely. Lack of information may apply for this situation.

Note: AEs with causality 'likely' or 'not assessable' are considered to be 'possibly drug-related.'

Adverse event reporting

Any adverse events (AEs) will be reported to the PI within 72 hours of notification of the event. The PI will notify the IRB of any major adverse events. Any unanticipated problems involving risk to the participants or others will be discussed with the PI and IRB. Non-serious AEs and incidences of noncompliance with the protocol will be reported to the IRB at the time of annual review.

Serious Adverse Events (SAEs) will be reported according to the following procedure:

The occurrence of serious adverse events will be reported to the Investigator within 24 hours after notification of their occurrence. The Investigator will report SAEs to the Vanderbilt Institutional Review Board within 7 days of the Investigator's notification of the event.

In an unanticipated event of prolonged side effect, requiring prolongation of hospital stay, patients will be retained in the hospital until side effects have resolved. For minor side effects, where inpatient care is deemed unnecessary, follow- up will be maintained via phone or as outpatient if necessary. Patient and their families will be given the PI's contact number for reporting any other effects of medication following discharge.

Any newly discovered information which may affect the subject or their caregiver's decision to continue to participate in the study will be passed on to them as soon as possible. This may also result in a change to the consent form and review by the IRB.

9.0 Study Withdrawal/Discontinuation

Participants may withdraw from the study at any time by informing the study staff verbally or in writing. If an individual withdraws their consent, we will withdraw the participant. Contact information for the PI and study staff will be made available to the participant upon enrollment in the consent document. Any remaining biological samples and data will be destroyed. Any data or biological samples that have been used for research prior to their withdrawal request will not be withdrawn and destroyed.

A participant may be withdrawn from the study by the PI if any of the following occurs:

i. A procedural complication occurs prior to completion of the study protocol that requires the study procedure to be aborted, or precludes collection of study data.

ii. The patient becomes hemodynamically unstable for any other reason that requires the study procedure to be cancelled prior to completion of the study protocol, or precludes the collection of study data

iii. The primary operator determines it is in the patient's best interest to forego completion of the study protocol

10.0 Statistical Considerations

Baseline clinical characteristics will be described using frequency and percentage for dichotomous variables and median with interquartile range for continuous variables. The design of this study is a crossover trial between "no treatment" and "atropine treatment". The primary outcome variable is a continuous variable measuring the number of beats of ventricular ectopy. The null hypothesis is that no difference exists between the "no treatment" and "atropine treatment" interventions in the number of beats of ventricular ectopy. The primary analysis will use a Wilcoxon-signed ranked test. A P-value <0.05 will be used to reject the null hypothesis. A secondary outcome will be measurement of complex ventricular ectopy defined as couplets or greater. Comparisons will be made between the "no treatment" and "atropine treatment" groups using: 1) the number of runs of complex ventricular ectopy (continuous variable) using the Wilcoxon-signed ranked test; and 2) the presence of complex ventricular ectopy (yes/no) using McNemar's test. As a pilot study, we may be underpowered to detect our primary analysis, but valuable data regarding the effect size and confidence intervals will be obtained to provide sample size estimations for subsequent larger scale clinical trials.

11.0 Privacy/Confidentiality Issues

We describe here mechanisms in place at Vanderbilt through IRB policy to protect against such risks; these apply to all studies described below. All records are retained on password-protected computers accessible only to members of the study team. Computers containing these records are only connected to networks if they include appropriate firewalls and security measures. The identity of any individuals and their families are not to be revealed in any publication without their written informed consent.

12.0 Follow-up and Record Retention

The expected duration of this study is estimated to be 4 years. The study results will be retained for at least six years after the study is completed. At that time, the research information not already in the medical record will be destroyed.