Pause-induced Ventricular Tachycardia: Clinical Characteristics

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A. Study Purpose and Rationale

Until three decades ago, ventricular arrhythmias were thought to be rare in occurrence and their natural histories unknown. With the advent of intensive care unit monitoring, long-term ambulatory electrocardiographic (ECG) recordings and implantible cardioverter defibrillators (ICDs), ventricular arrhythmias have been diagnosed more frequently, especially in patients with structural heart disease.[14] The incidence in patients post-myocardial infarction has been shown to be from 10-20% depending on the time elapsed since infarction, and the mortality rates can be as high as 75% in 1 year for patients with sustained monomorphic ventricular tachycardia (MMVT) and 40% in 5 years for patients with unsustained VT (MUST trial). The current medical treatments available are thought to be effective in suppressing ventricular arrhythmias only 30-40% of patients. Unfortunately, many of these same therapeutic modalities can exacerbate this arrhythmia. ICDs have been shown to prolong survival in patients with ventricular arrhythmias by prevention of sudden death (AVID trial), but mortality at 3 years is still 25%, versus 35% for patients on Class III antiarrhythmics agents. Because of the high incidence of ventricular arrhythmias, and the high mortality rates conferred upon patients with these arrhythmias, better understanding of the mechanisms of onset and better therapeutic modalities need to be addressed.

Reentry, triggered activity, or abnormal automaticity are three major categories of arrhythmia mechanisms thought to be responsible for the generation of ventricular arrhythmias.[6] The contribution of a particular mechanism depends on the type of cardiac disease as well as dynamic factors such as coronary ischemia, medications, electrolyte disturbances, and autonomic influences[1,13] As is noted by Anderson, et al.,[6] reentry is widely believed to be the mechanism of ventricular tachycardia because of reproducible initiation and termination by programmed stimulation in traditional electrophysiological studies (EPS). However, the classic mechanisms described may not account for spontaneous arrhythmias that have been observed, and the pattern of initiation of spontaneous ventricular tachycardia may distinguish patients who may respond differently to EPS studies or medications. As Anderson suggests, "greater emphasis should be placed on the capture and analysis of spontaneous arrhythmias so that their properties may be incorporated into more representative and comprehensive models of arrhythmogenesis, which will provide better prediction and treatment of life-threatening arrhythmias."

The progress in implantible cardioverter defibrillator (ICD) technology has improved the diagnostic and therapeutic efficacy of these devices in the management of ventricular tachyarrhythmias. Electrical events can be recorded both before and after the device has either delivered therapy or aborted it. These recorded electrograms allow more accurate characterization of the initiation of an arrhythmic event. Recognition of specific electrogram patterns of initiation of ventricular tachycardia (VT) could provide better understanding of the electrophysiologic mechanisms inherent in these arrhythmias, and may lead to better diagnostic and therapeutic interventions. Several studies have analyzed the mechanism of onset of ventricular tachyarrhythmias based on both retrospective and prospective evaluation of ambulatory electrocardiography as well as intracardiac electrograms[1,2,4-6,7,10-12]. They are limited by the small number of patients included in each study, by the evaluation of all episodes recorded – so that most of the data came from a subset of the studied patients, by limiting studies to only one type of ventricular tachyarrhythmia (monomorphic VT, polymorphic VT or ventricular fibrillation), and by inadequate characterization of patients at risk for certain mechanisms of onset.

The present study is proposed to gain insight into the mechanism of initiation of spontaneous VT by analyzing stored intracardiac electrograms from patients with ICDs.

Torsades de pointes, which is a form of ventricular tachycardia, occurs in the setting of QTc prolongation and has been shown to have a typical "long-short" initiating sequence. [7,10,11] As Cranefield notes, [9] ventricular arrhythmias may not necessarily assume the classic 'torsades' appearance (twisting of the points) and may be designated polymorphic VT, and even monomorphic VT may alternate with a 'torsade pattern'. In several studies, the long-short initiation cycle has been noted in monomorphic VT [4,5] (occurring in 6.6% and 14% of recorded MMVT events) and ventricular fibrillation. [7] There are no studies to date, however, that look at pause-induced VT in a wide spectrum of patients with different types of cardiac disease and its occurrence within all types of ventricular arrhythmias. A number of investigators have suggested that the mode of initiation of VT may be most important in guiding optimal therapy. [8,12] Pause-induced VT may be a clinical entity that, if recognized and characterized, may confer its own risks and indications for treatment.

Saeed, et al. [1] suggested that pts with pause-induced monomorphic VT are more likely to have coronary artery disease, but was not powered to show this. Bigger, et al[3] showed that more complex arrhythmias and lower ejection fraction (EF) conferred high risk of mortality in patients who were post-myocardial infarction. The CASCADE and ESVEM trials suggest that Class III agents are more effective than Class I agents in treatment of ventricular arrhythmias. A small study of patients with polymorphic VT also suggests that amiodarone to be more effective in controlling arrhythmia than Class I agents.[2] These studies suggest a number of clinical characteristics that would typify patients with pause-induced VT, and may provide strategies for more optimal treatment of this arrhythmia.

B. Hypothesis

The long-short initiating cycle typically described in Ventricular Fibrillation/Torsades occurs in other types of Ventricular Tachycardia (VT) as well, and occurs more frequently than previously described. The patients with this pause-induced VT are more likely to have coronary artery disease (CAD), and a lower EF (<0.20) than patients with other types of VT. Patients with pause-induced VT are also more likely to be on Class I agents (quinidine, procainamide, mexilitine) and not on Class III agents (amiodarone, sotalol) than patients without ventricular arrhythmic events.

C. Methods

a. Study Design

This is a prospective observational study of all patients followed at the ICD clinic at Columbia Presbyterian Hospital. 320 patients will be enrolled (see below for sample size calculation) after discussion and approval from their primary care physicians, as well as upon their own consent. These patients are already routinely followed every 3 months in the clinic to monitor the functioning of the ICDs, the patients' possible arrhythmia symptoms, their tolerance of cardioactive medications and to interrogate the ICD for arrhythmic events. On the first routine clinic visit after enrollment in the study, certain baseline data will be obtained: electrocardiogram and echocardiogram. Both of these tests are routine and non-invasive. Routine clinic data will also be collected: the patients' medications, and any changes that have been made to the patients' regimen, and the type of cardiac disease (which will already be documented). Additionally, ICD interrogation is performed every 3 months at the ICD clinic. The defibrillator records any arrhythmic events that have occurred over this time period, and can print out a 2-lead electrogram of the event, as well as electrical activity both before and after the event. If the patient has had an episode of a sustained ventricular tachyarrythmia, the event will be printed out and evaluated, which will be the endpoint for that patient in the study. Otherwise, the patient will continue to be followed in a standard fashion every 3 months in the clinic. The study will conclude in 4 years.

The conceptual outcome that will be followed will be an episode of a sustained ventricular arrhythmia. The first episode of VT only will be evaluated from the start time of study. This will avoid some of the problems of previous studies, where episodes alone were evaluated, and often only a few patients in a particular study had most of the arrhythmias evaluated. In evaluation of a patient's event, the

arrhythmia will be classified by type, and then the initiation sequence will be evaluated for the possibility of a long-short cycle. <u>VT definition</u>: QRS widening >0.12, increased HR >150 bpm, A-V dissociation, >30s duration or requiring intervention for termination.[14] The type of ventricular arrhythmia will be classified according to classic descriptions:

- MMVT: regular rate and consistent beat-to-beat morphology
- PMVT: frequent changes in QRS morphology occurring every 1-2 seconds
- VF: disorganized activity and no discernible QRS complexes, Torsades: (shifting axis every 1-2 seconds) [14]
- The short-long initiating sequence, or the identification of pause-induced VT, will be assessed via objective measurements of the initiating sequence, previously described:
- <u>sequence definition</u>: CI/CI(n-1) measured via electrogram, ratio <0.4 (prematurity index) and a premature extrasystolic beat at n-1 w/ post-extrasystolic pause, using the intervals measured by the ICD.[5]
- The clinical characteristics of these patients will be obtained and recorded at the initial clinic visit: the baseline ECG rhythm will be evaluated and the baseline QTc interval will be calculated. From the electrogram, the QTc at the time of the VT event will also be calculated. The ECHO will be noted and the EF recorded for all patients.

b. Statistical Analysis
1) The statistical methods that will be used to analyze the data will be several:
2) To establish that pause-induced VT occurs more frequently than described: Chi-square analysis comparing 0.2 (expected frequency in this study) vs. 0.10 (although this is an average of 2 studies only looking at MMVT, episodes vs. patients → so it is an estimate of what one might expect in this study)
3) To establish that patients with pause-induced VT will have higher frequency of CAD than patients with other types of VT: Chi-square analysis comparing 0.95 vs. 0.70.
4) To establish that patients with pause-induced VT will have lower EF than patients with other types of VT: unpaired T test 0.2 vs. 0.35
5) To establish that patients with pause-induced VT will be more likely to be on Class I agents and less likely to be on Class III agents than patients without ventricular arrhythmias: Chi-square analysis 0.9 vs. 0.3, and 0.1 vs. 0.6.
6) The baseline QTc and QTc at the time of arrhythmia will also be evaluated for possible prolongation of both, or the latter, comparing pause-induced VT vs. other types of VT for both using unpaired T test.

c. Sample Size
In order to determine the number of patients needed for this study:
1) 110 patients with VT events would be needed to see a higher frequency of pause-induced VT: this is inexact estimate, since available studies are looking at different parameters. 0.2 (expected proportion) against the constant (theoretical) 0.1 in this same population, Chi-square test divided by two because 0.1 is constant.
2) 120 pts with VT events needed to see CAD difference (Chi-square, power calculated in 4:1 ratio since only 20% expected to have pause-induced VT). 0.95 vs. 0.7 proportions
3) 52 patients with VT events needed to see EF difference (unpaired T-test, power calculated in 4:1 ratio) proportions 0.2 vs. 0.35 with 0.15 standard deviation.
4) 82 total patients for Class I agents, and 110 total patients for Class III agents difference. (Chi-square analysis, power calculated in 37:3, or 12.3:1 ratio for number of pause-induced VT vs. patients without ventricular arrhythmias) 0.9 vs. 0.3 and 0.1 vs. 0.6 proportions

From my brief retrospective study of patients in the ICD clinic, the VT event rate was approximately 37.5% over 4 years (15/40 patients). Of these events, 20% are initiated by a long-short

sequence (3/15 patients). The VT event rate corresponds to other studies, but pause-induced VT is higher in frequency.

The largest number of patients needed to power this study adequately is the required number to look at whether patients with pause-induced VT have a higher frequency of CAD than patients with other types of VT. 120 patients with VT events would need to be enrolled, which means 320 patients total would need to be followed in the study for 4 years. (This is calculating a 37.5% event rate over 4 years).

D. Subjects Selection

All patients followed at the ICD clinic every 3 months.

Patients will be excluded if the ICD has inadequate baseline data preceding an event. Also, patients who do not meet AHA guidelines for ICD implantation will be excluded (there are patients enrolled in investigational studies who are followed in the clinic).

Patients will be recruited through the ICD clinic registry. The investigators will contact the patients' primary care physicians for approval and approach of the patient for inclusion in the study. The patients will consent to the study and be assigned a unique code number at that time, under which all data will be recorded.

E. Miscellaneous/ outstanding issues

Description of study procedures:	none will be performed
Study drugs:	none – medications will be documented but not changed
Medical devices:	ICDs will have been implanted for AHA guideline indications before pts are eligible for this study
Study questionnaires:	none
Confidentiality of study data:	patients will be assigned numbers to maintain confidentiality if data is to be published, otherwise no anticipation of issues
Risks and benefits:	observational study, no anticipated ethical difficulties (no benefits nor risks to patients)
Alternative therapies	none
Compensation and costs to subjects:	none – follow-up at clinic q 3 months is already routine care as part of ICD management
Minors as research subjects:	none
Radiation or radioactive substances:	none

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