Defining the Pattern of Initiation of Monomorphic Ventricular Tachycardia Using the Beat-to-Beat Intervals Recorded on Implantable Cardioverter Defibrillators from the RAFT Study: A Computer-Based Algorithm

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A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Master of Science

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August 2017

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References
Monomorphic ventricular tachycardia (VT) is a common event in patients with heart failure and reduced ejection fraction (EF). The study of the transition between the baseline rhythm and the tachycardia – initiation of the tachycardia – may help to understand the mechanism of the tachycardia, potentially having prognostic impact. Although many studies had been published addressing this feature, prognostic and possible therapeutic value were never demonstrated.

From the first studies, at least two different patterns of initiation were defined based on the morphology of the beat initiating the VT compared with the morphology of the VT classifying the pattern of initiation of the VT as non-sudden, when the morphology of the beat initiating the VT is different of the morphology of the VT, and sudden, when they are similar.

The initiation of the tachycardia is a feature that has not been studied in large data sets, mainly given the lack of availability of the morphology of the beat initiation the VT. A computer based algorithm was developed to classify the initiation of the tachycardia based on the beat-to-beat intervals, allowing the analysis of pre-existing datasets.
Résumé

Les tachycardies ventriculaires (TV) monomorphes sont des événements courants chez les patients atteints d'insuffisance cardiaque avec fraction d'éjection (FE) altérée. L'étude de la transition entre le rythme de base et la tachycardie - l'initiation de la tachycardie - pourrait aider à comprendre le mécanisme de cette tachycardie, ce qui pourrait avoir un impact sur le pronostic.

Les premières études ont permis de définir au moins deux différents modes d'initiation en se basant sur la morphologie du battement initiant la TV comparé à la morphologie de la TV, classant ce mode d'initiation de la TV en "non-subit", quand la morphologie du battement initiant la TV est différente de la morphologie de la TV, ou "subit", lorsqu'elles sont identiques.

L'initiation de la tachycardie est un élément qui n'a pas été étudié sur de grands ensembles de données, principalement parce que la morphologie du battement initiant la TV n'était pas une donnée enregistrée. Nous avons développé un algorithme informatisé pour classer l'initiation de la tachycardie en se basant sur une analyse des intervalles battement par battement, permettant l'analyse a posteriori de bases de données pré-existentes.
Preface

The present thesis has been written as a manuscript based thesis in accordance with the regulations put forth by the Faculty of Graduate Studies and Research, McGill University.

The first chapter entitled *Pattern of Initiation of Monomorphic Ventricular Tachycardia and Implications on Tachycardia Mechanism*, was published in Minerva Cardioangiologica volume 65, issue 4, pages 357-368 August 2017 and represents a comprehensive literature review about the subject. The second chapter entitled *Defining the Pattern of Initiation of Monomorphic Ventricular Tachycardia Using the Beat-to-Beat Intervals Recorded on Implantable Cardioverter Defibrillators from the RAFT Study: A Computer-Based Algorithm* is in the process of submission in the Journal of Electrocardiology as a technical paper. The unusual sub-division in chapter 2 is due to the requirements of the mentioned journal for this type of paper.
Acknowledgements

My sincere gratitude goes in first place to my supervisor to Dr. Vidal Essebag.

I am thankful to his encouragement, support and guidance which helped in successfully completing this project work.

The present thesis is a product of a work group formed by the Electrophysiology department at McGill University Health Center and McGill Physiology department. The completion of this project would be impossible without the different skillsets gathered in this team I was thrilled to be part of. My deep gratitude to Leon Glass, Riccardo Proietti, Alvin Shrier, Lyndon Sobolik, Zhubo D. Zhang, Dr. Ahmed Al-Turki, Dr. Guillaume Viart and Dr. Barry Burstein.

Finally I woud like to thank my beloved wife, Raphaela and My son Daniel who have provided me moral and emotional support through this “adventure” in this friendly, amazing and super cold land called Canada.
Author Contributions

Dr. Vidal Essebag, Dr. Riccardo Proietti, Alvin Shrier and Leon Glass gave a significant contribution to the development of the original idea. Lyndon Sobolik and Zhubo D. Zhang were responsible for the development of the software and writing the computer based algorithm under supervision of Leon Glass. Dr. Ahmed Al-Turki and Dr. Guillaume Viart were responsible for part of the data extraction. Dr. Barry Burstein and Michelle Samuel greatly contributed with editorial review of the manuscripts.

Dr. Rodrigo Barbosa gave important contributions to the development of the original idea, literature review, data extraction and was responsible for writing both manuscripts.
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<td>congestive heart failure</td>
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<td>CL</td>
<td>cycle length</td>
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<td>CRT</td>
<td>cardiac resynchronization therapy</td>
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<td>DADs</td>
<td>delayed after-depolarizations</td>
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<td>EP</td>
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<td>implantable cardiac defibrillator</td>
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<td>ICMP</td>
<td>ischemic cardiomyopathy</td>
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<td>MI</td>
<td>myocardial infarction</td>
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<td>NICMP</td>
<td>non-ischemic cardiomyopathy</td>
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<td>PVCs</td>
<td>premature ventricular contractions</td>
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<td>SCD</td>
<td>Sudden cardiac death</td>
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<tr>
<td>UTAS</td>
<td>unrelated to abnormal substrate</td>
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<td>VF</td>
<td>ventricular fibrillation</td>
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<td>VT</td>
<td>ventricular tachycardia</td>
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Chapter I

Pattern of Initiation of Monomorphic Ventricular Tachycardia and Implications on Tachycardia Mechanism

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ABSTRACT:

The incidence of sudden cardiac death, predominantly caused by ventricular tachycardia and ventricular fibrillation, is high in patients with congestive heart failure. Implantable cardiac defibrillators have improved survival in this population but defibrillator shocks can lead to low quality of life and heart failure progression. The current management of recurrent ventricular tachycardia includes ablation and anti-arrhythmic drugs and both are associated with high recurrence rates. Better understanding the mechanism of ventricular tachycardia allowing individualization of treatment may improve outcomes.

Re-entry is currently accepted as the mechanism of the majority of monomorphic ventricular tachycardias in patients with congestive heart failure, being responsible for more than 90% of the ventricular tachycardia in patients with ischemic cardiomyopathy. On the other hand, some studies show a greater participation of focal arrhythmias in the genesis of ventricular tachycardia in this population.

The pattern of initiation of ventricular tachycardia is divided into sudden, when the first beat of the tachycardia is morphologically similar to the rest of the tachycardia, and non-sudden, when its morphology is dissimilar. An association between the pattern of the initiation and the mechanism of ventricular tachycardia has been proposed.

The pattern of initiation of ventricular tachycardia is a readily available from data stored in current generation implantable cardiac defibrillators. The association with tachycardia mechanism may allow individualization of the therapy, however evidence is lacking and further research is required.

Key words: Ventricular Tachycardia - Structural Heart Disease - Arrhythmia Mechanisms - Initiation Pattern
INTRODUCTION:

Sudden cardiac death (SCD) is one of the leading causes of death in developed countries. In 2014, it represented more than 50% of the cardiac deaths in the United States, with an incidence of 76 per 100,000 persons per year (approximately 230,000 cases).[1] In the past 30 years, there has been a shift observed in the predominant rhythm recorded in cardiac arrest. Whereas ventricular tachycardia (VT) and ventricular fibrillation (VF) previously accounted for approximately 70% of the recorded rhythms, they currently account for 20-25%.[2] Patients with reduced left ventricular ejection fraction (EF) are at a high risk of SCD and the majority of these deaths are secondary to VT and VF.[3]

The implantable cardiac defibrillator (ICD) was developed to reduce the incidence of SCD. An ICD was first implanted in a human subject in 1980 [4]. After demonstrating the efficacy of the ICD in terminating VT and VF, as well as its capacity to prevent all-cause mortality when used as secondary prevention[5-8], the focus shifted to prevention in patients at risk of SCD but with no prior event. In 1996 the Multicentre Automatic Defibrillator Implantation Trial Investigators (MADIT) published the first primary prevention study demonstrating a mortality reduction in patients with ischemic cardiomyopathy (ICMP) who were at high risk for SCD, defined as left ventricular EF ≤ 35%, non-sustained VT on Holter monitor or inducible VT with programmed ventricular stimulation not supressed by procainamide. [9] Subsequently, Buxton et al., demonstrated that electrophysiological (EP) study guided therapy reduced mortality in high risk patients (ICMP at least 4 days after the last myocardial infarction (MI), left ventricular EF ≤ 40%, non-sustained VT on Holter monitor, and inducible VT with programmed ventricular stimulation), mainly as a result of ICD implantation.[10] In 2002, Moss at al., using the left ventricular EF ≤ 30% as the only risk
factor for SCD in subjects with ICMP, demonstrated a 31% all-cause mortality reduction in the ICD arm compared with the standard medical treatment.[11] With a robust evidence base demonstrating a benefit of ICD therapy in patients with ICMP, the focus became primary prevention in patients with non-ischemic cardiomyopathy (NICMP). A randomized trial including 458 patients with NICMP, left ventricular EF ≤35% and non-sustained VT or premature ventricular contractions (PVCs) on Holter monitor, comparing ICD with standard medical therapy showed a 35% mortality reduction in the ICD group, without reaching statistical significance. [12] In 2005, a randomized trial comparing ICD vs. amiodarone included ischemic and non-ischemic patients with LVEF ≤ 35% and symptomatic congestive heart failure (CHF). There was a 23% mortality reduction in the ICD arm. In the sub-group analysis, patients with NICMP had a 27% mortality reduction without reaching statistical significance.[13] A meta-analysis of 1854 patients with NICMP showed a 31% mortality reduction with ICD compared with medical treatment alone. [14] This evidence served as the basis for indications for ICD as primary prevention: Patients with ICMP and left ventricular EF ≤ 30% have a class I indication for ICD even if asymptomatic. ICD has also a class I indication in patients with symptomatic heart failure, ischemic or non-ischemic cardiomyopathy and left ventricular EF ≤35%.[15-17] Another recent randomized controlled trial of patients with NICMP, symptomatic CHF and left ventricular EF ≤35% showed that, compared with the standard medical therapy, patients who received an ICD had a 13% mortality reduction without reaching statistical significance. In this trial, the standard medical therapy included cardiac resynchronization therapy (CRT) when indicated, and adherence to beta-blockers and ACE-inhibitors was greater than in previous trials.[18]

ICD has become a standard treatment for either primary or secondary prevention of sudden cardiac death.[19] A 2009 survey performed in 61 countries found 328,027 ICD
implants, representing a significant increase compared with the same survey data from 2005. [20, 21]

ICD shocks have been shown decrease quality of life [22, 23] and ICD therapies have the potential to increase mortality. A randomized trial analysing ICD programming to avoid shocks by prolonging detection or increasing the detection rate demonstrated a reduced mortality compared with a standard ICD programming.[24] A meta-analysis of 2 prospective studies and 4 randomized controlled trials showed reduced mortality with therapy reduction ICD programming when compared with conventional programming.[25] A more recent meta-analysis also demonstrated an increased mortality for patients who received ICD shocks (appropriate, inappropriate or both) when compared with patients who did not receive a shock. [26] The hypothesized physiological explanation is that ICD shocks cause cellular damage, which can lead to progressive heart failure. Such damage had been demonstrated pathologically and by elevation of cardiac enzymes.[27, 28] Therefore, strategies to prevent VT and VF are desirable even when an ICD is in place.

Antiarrhythmic drugs have been shown to reduce ICD shocks but the results are very heterogeneous. In one trial including patients with secondary prevention ICD and LVEF ≤40%, amiodarone plus beta-blockers was superior to beta-blockers alone or sotalol in preventing ICD shocks after one year of follow-up. There was a trend towards superiority of sotalol when compared with the beta-blockers alone with no statistical significance. Both antiarrhythmic drugs had a higher rate of drug discontinuation and amiodarone was associated with a higher incidence of adverse thyroid and pulmonary events, as well as symptomatic bradycardia [29]. In a 2015 Cochrane meta-analysis, 4 studies compared class
III antiarrhythmic drugs with beta-blockers in the prevention of ICD shocks. Amiodarone and sotalol showed no difference in appropriate ICD shocks and therapies. [30]

Ablation of ventricular tachycardia is also effective in preventing ICD shocks. [31, 32] Studies of prophylactic substrate-based VT ablation in patients with ICDs demonstrated a reduction of ICD therapies and ICD shocks when compared with ICDs alone in patients with a previous MI. [33] Another study randomized patients with prior MI, documented stable VT and LVEF ≤50% to ablation plus ICD or ICD alone. The primary outcome, time to first recurrence of VT or VF, was greater in the ablation group. [34] A recently published randomized controlled trial of patients with ICMP and VT who failed antiarrhythmic therapy compared ablation to an escalation of antiarrhythmic medications and showed a reduction in the composite primary outcome of death, ICD shock and VT storm, with ablation therapy. [35] Of note, the rate of this primary outcome was considerably high for both groups (68.5% versus 59.1%), underscoring the severity of the disease and the need for better therapy in this population.

Understanding the VT mechanism in each patient could help tailor the treatment and potentially improve outcomes. There are several different mechanisms for VT in patients with CHF: 1) a myocardial scar can serve as a substrate for re-entry as the diseased tissue can have functional lines of block; 2) the change in ionic channel density and action potential duration, as well as myocardial stretch in patients with reduced left ventricular EF can favour focal VTs; 3) patients with CHF are also susceptible to focal VTs unrelated to the abnormal substrate. [36-41] Currently, there is no available method to discern the mechanism of a clinical VT unless it can be induced and sustained during an EP study. The current guidelines for treatment of VT do not take into consideration the mechanism of the
tachyarrhythmia in patients with CHF.[42] When the arrhythmia is not hemodynamically tolerated, especially in patients with a prior MI, it is often assumed to be re-entrant and the ablation strategy is focused on regions with electrophysiological properties associated with re-entry channels.[43-46]

The initiation of a VT episode can provide important clues about its mechanism. It is often classified in two distinct patterns: 1) sudden – when the morphology of the first beat of the tachycardia matches the subsequent beats, and 2) non-sudden – when the first beat of the tachycardia is morphologically different from the other beats [47]. Those characteristics can be readily accessed in patients with ICDs and have the potential to provide valuable information, leading to a better understanding of the tachycardia and ultimately a better treatment strategy.

This comprehensive review of the literature was designed with a focus on the pattern of initiation of monomorphic VT and its potential relationship with the VT mechanism.

MECHANISM OF VENTRICULAR TACHYCARDIA IN PATIENTS WITH HEART FAILURE:

PATHOPHYSIOLOGY

Cardiac arrhythmias can be caused by abnormal impulse formation giving rise to a focal arrhythmia, or abnormal impulse conduction generating a re-entrant rhythm. The focal arrhythmias, according to the phase of the cardiac cycle during which the abnormal impulse is generated, can be further sub-divided into: 1) enhanced automaticity; 2) triggered activity due to early after-depolarizations (EADs); and 3) triggered activity secondary to delayed after-depolarizations (DADs). All of the described mechanisms may contribute to the pathogenesis of VT in patients with reduced LVEF.[48, 49]
Anatomic re-entry as a potential mechanism for cardiac arrhythmias was first described in 1913 by George Ralph Mines.[50] Since that time, it has been thoroughly investigated, and conditions for its occurrence have been postulated: adjacent tissue or pathways should have different refractory periods and must be joined proximally and distally from what are known as “limbs” of the tachycardia. A premature depolarization must encroach on the refractory period of one of the limbs (unidirectional block), conducting solely over the remaining limb. The conduction velocity in this limb has to be slow enough to allow for recovery of refactororiness of the previously blocked pathway. The sum of the length of the limbs must be longer than the wavelength of the tachycardia, which is defined by the conduction velocity multiplied by the effective refractory period of the tissue. This allows the electrical impulse to spin around the circuit without encroaching on its refractory period. [48, 51] The scarred myocardium in patients with reduced left ventricular EF can potentially satisfy all these conditions, serving as a substrate for VT.

Histologic and ultra-structural analysis of resected endocardium and sub-endocardium of patients with prior MI and recurrent VT demonstrated bundles of myocardial cells embedded in connective tissue. The viable myocardial cells contained various degrees of degenerative changes ranging from focal loss of myofibrils and thickening of Z-bands, aggregated segments of dilated sarcoplasmic reticulum and cytoskeletal filaments, and near-complete loss of the myofibrils with replacement of mitochondria by glycogen particles and lysosomal inclusion bodies. Less than 5% of the cells had a completely normal appearance.[36] De Bakker et al. studied impulse conduction in perfused papillary muscles extracted from hearts of patients who had undergone heart transplantation for end-stage ICMP. They described a “zigzag” impulse propagation that could increase the length of the route along which activation has to travel, and therefore
reduce conduction velocity. [37] In NICMP, a down-regulation of gap junctions was found to be a possible explanation for decreased conduction velocity in a model of pacing-induced cardiomyopathy.[52]

The demonstration of a histologic substrate established the evidence basis for re-entry as a mechanism for VT in patients with reduced left ventricular EF. [53, 54] Identification of the underlying electrophysiological properties of re-entry circuits allowed for the development of different treatment strategies. [43-46]

In contrast to re-entry circuits, the pathophysiology of focal arrhythmias in patients with reduced LVEF is not well studied. An experimental study of healthy canine hearts was able to produce premature ventricular complexes and short runs of non-sustained VT by stretching the heart with a servo-controlled pump. [39] The stretch caused by volume overload and increased end diastolic pressure could contribute to PVCs that serve as a trigger for re-entry and sustained focal VT’s. In another canine model of ICMP, Pogwizd was able to define the mechanism of spontaneous PVCs and non-sustained VT using three-dimensional maps with up to 232 intra-mural sites. With continuous mapping for 60 minutes for each dog, they were able to determine the mechanism of 31 PVCs, 45 ventricular couplets, and 99 beats of VT. All the mapped beats were found to be focal.[55] Using the same model, this group analyzed the mechanism of VT induced by programmed ventricular stimulation with and without isoproterenol. They were able to induce sustained VT in 5 out of 8 dogs (3 at baseline and 2 with isoproterenol). All the VTs were determined to be focal. [56]

A number of changes in ion channels and their respective currents can predispose the failing heart to focal arrhythmias. Downregulation of inward potassium currents,
defective sequestration of calcium by the sarcoplasmic reticulum, upregulation of the sodium-calcium exchanger, and an increase in the late sodium current ultimately contribute to a prolongation of the action potential duration. This, in turn, can precipitate L-type calcium channel reactivation and, consequently, early after-depolarizations (EAD). T-type calcium channels, shown to have an increased density in heart failure models, can be activated in hyperpolarized states and potentially lead to enhanced automaticity. [57] Ryanodine receptors, despite being downregulated in failing hearts, are leaky, resulting in a diastolic escape of calcium, activation of the sodium-calcium exchanger, and a propensity to induce delayed after-depolarizations.[57]

**DEFINING THE MECHANISM OF CLINICAL VT**

The EP study is the gold standard for defining the mechanism of an arrhythmia of interest. The ability to reset an arrhythmia with extra stimuli from a distant site is a hallmark of re-entrant rhythms [58, 59] and continuous resetting with fusion, known as entrainment, is only possible in re-entrant arrhythmias. In brief, with continuous pacing from a distant site at a cycle length (CL) shorter than a focal arrhythmia CL, the wave fronts will collide progressively closer to the arrhythmia focus until the pacing wave front reaches the focus with suppression of the rhythm and fusion will no longer be seen. On the other hand, in a re-entrant rhythm, the paced wave front will penetrate the circuit and continuously advance the circuit, giving rise to a steady state of fusion. Practical criteria were established to demonstrate re-entry during an EP study: 1) straight pacing with a faster CL during the tachycardia yields constant fusion on the surface leads, except for the last captured beat which is not fused; 2) pacing at different CLs will demonstrate different degrees of fusion, with faster pacing rates causing more myocardial depolarization by the pacing spike and the
resulting surface lead morphology will be more similar to the paced morphology; 3) if the site of block manifests during the pace termination of a tachycardia, then the first paced beat after the termination will lead to activation in a different direction; 4) change in conduction time and electrogram morphology when pacing at 2 different rates. [60-63] If one or more of these criteria are present, a re-entrant rhythm is confirmed. Other properties can further help to distinguish a re-entrant from a focal rhythm, such as mapping the wave front of activation to demonstrate radial spread in focal arrhythmias, or visualization of continuous activity through the whole cycle length (CL) in re-entrant arrhythmias. The reproducible initiation and termination of the arrhythmia with premature extra stimuli is also a hallmark of re-entrant rhythms.[51]

The advent of the EP study allowed for a greater understanding of the mechanisms underlying VT. In 1972, the first case series was published describing 5 patients with recurrent ventricular tachycardia undergoing EP study, 4 of them had ICMP and 1 had a previous myocarditis. Physicians could reproducibly initiate the VT in all patients with programmed ventricular stimulation favouring a re-entrant mechanism. [64] In 1976, another case series was published with 17 patients (6 ICMP, 6 idiopathic VT, 4 dilated cardiomyopathies and 1 valvular disease). They were able to reproducibly initiate the tachycardia in only 2 patients, favouring a focal mechanism. [65] A third case series published in 1978 studied 21 patients with different underlying heart disease and showed a reproducible initiation with programed ventricular stimulation in 19 patients, suggesting re-entrant mechanism. [66]

The complexity of VT was probably underestimated in the earlier studies as they had attempted to define a single mechanism among patients with different underlying
athologies. As the knowledge evolved, different types of ventricular tachycardia were described as well as their respective mechanisms. Re-entrant VTs were associated with myocardial scars and ICMP. Furthermore, continuous activation through the whole cycle length was mapped.[53, 54] In addition, re-entry was found to be the mechanism of a specific type of VT using the His-Purkinje fibres in structurally normal hearts characteristically sensitive to verapamil. [67]

Focal monomorphic VTs associated with structurally normal hearts, known as idiopathic VTs, have been extensively described. In approximately 10% of the VTs, an underlying myocardial substrate cannot be found. [68]. The most common sites of origin are the right ventricular outflow tract, left ventricular outflow tract and aortic cusps. [69] Other less frequent sites are papillary muscles,[70] Purkinje fibres and the mitral annulus. Initial findings demonstrating termination of idiopathic VT with adenosine and beta-blockers suggested cAMP-mediated activity as a possible mechanism.[71, 72] Currently it is believed that DADs are the cause to this type of VT. The mechanism is linked to intracellular calcium overload and can be inhibited by adenosine, beta-blockers and calcium-channel blockers. It is precipitated by isoproterenol and exercise.[48]

It is currently accepted that re-entry is the mechanism for the vast majority of the monomorphic ventricular tachycardia in patients with ICMP.[51] In the majority of cases, current techniques for ablation of VT in these patients are based on identifying and ablating potential channels for re-entry when the patient is in sinus rhythm. [31, 43-46, 68]

Few studies have focused on focal VTs in patients with underlying structural abnormalities. In a case series published in 1992, 13 patients with a previous MI and recurrent VT undergoing surgical endocardial resection were analysed. [73] Transmural
intra-operative 3D activation maps were obtained using plunge needle electrodes. Up to 156 recordings sites were registered for each patient. Out of 17 induced VTs, the data was sufficient to determine the mechanism for 10. Fifty percent of the VTs were found to be focal, despite fixed, functional conduction block and delay demonstrated in the EP study. In 1998, 6 cases of end-stage NICMP undergoing heart transplant were described. During transplant surgery, up to 156 intramural electrodes were placed with plunge needles. Ventricular programmed stimulation was performed for 15 minutes. Nineteen VTs (74 VT beats) were induced. 6 PVCs, 1 couplet, and 1 three-beat VT (a total of 11 ventricular beats) occurred spontaneously and were mapped. All the induced and spontaneous beats were focal. These sites exhibited a variable degree of interstitial fibrosis, ranging from no fibrosis to extensive fibrosis.[74]

More recently, in a retrospective study of 249 patients referred for VT ablation, focal VT unrelated to abnormal substrate (UTAS) was found in 97 patients (39%). Non-re-entrant tachycardia UTAS was defined as focal VT without an underlying substrate or when the site origin of the VT was different from the known substrate. The remaining 61% had either re-entrant VT or focal VT coming from a known substrate. The analysis of the 97 focal VTs showed that 42 patients had an abnormal substrate, defined as: 1) low left ventricular EF that did not normalize after successful ablation or 2) known underlying substrate, such as arrhythmogenic right ventricular cardiomyopathy, hypertrophic cardiomyopathy, cardiac sarcoid, severe valvular disease with or without late gadolinium enhancement on cardiac magnetic resonance, or low-voltage areas on electro-anatomic mapping. Comparing patients with and without underlying substrates, differences in arrhythmia location were found, as well as a larger number of multiple non-reentrant UTAS and additional non-
idiopathic VT in the group with abnormal substrate. A significant 5.1% increase in the left ventricular EF was noted after ablation. [41]

INITIATION OF VENTRICULAR TACHYCARDIA:

The first studies registering the onset of ventricular tachyarrhythmias were based on retrospective evaluation of ambulatory electrocardiography. In 1981, five patients with left ventricular dysfunction on quinidine were reported to have VF while wearing a Holter monitor. In all five patients, the rhythm initiating the SCD event was polymorphic VT compatible with torsades de pointes, which further degenerated into VF. All patients had a long QT interval preceding the event. [75] A similar series of 12 patients with torsades de pointes and VF was subsequently published. [76] In 1984, Josephson et al. published a series of 27 patients in which the moment of the SCD was recorded on a Holter monitor. In 20 patients, the final event was a tachyarrhythmia (VT/VF). Bradyarrhythmia was recorded in 7 patients. In all the patients with tachyarrhythmias, the events were initiated by VT (14 monomorphic VTs and 6 polymorphic VTs). Polymorphic VT characterized as torsades de pointes was observed in 2 patients, and 4 patients had degeneration of the VT into VF. The VT was initiated by a short-coupled PVC (R on T) in 3 patients, and 2 patients had a “long-short” phenomenon initiating VT. [47] They observed an increase in the frequency of premature ventricular contractions in the hour preceding the event in 15 patients and an increase in heart rate from a mean of 78.6 ± 11.6 beats/min during the first hour of monitoring to 96.4 ± 8.2 beats/min in the last hour of monitoring, with an increase greater than 20% of the baseline heart rate in 11 patients. [77] In a series published by Milnes et al., 13 episodes of cardiac arrest were recorded on Holter monitor. VT was the arrhythmia initiating the events in 12 patients, with degeneration into VF in 10 patients. Bradycardia
followed by immediate VF was observed in 1 patient. An increase in the number of VT runs per hour was observed in the hour preceding the event in 10 patients. 2 patients had a short coupled PVC (R on T) as the initiating beat of the tachycardia.[78] A review of 7 case series including 157 cases of SCD registered on Holter monitor found tachyarrhythmias to be the initiating events in 83.4% of the patients and bradyarrhythmias in the remaining 16.6%. In 8.3% of the patients, VF was the culprit arrhythmia (often preceded by a single PVC or a short run of non-sustained VT). Ventricular tachycardia (VT) was the culprit arrhythmia in 62.4% of all patients (with or without degeneration into VF). Torsades de pointes was the culprit arrhythmia in 12.7% of the SCD cases. An increase in the baseline heart rate preceding the final event was a common observation among the studies.[79]. Overall, these series are limited by the unintentional registration of the arrhythmia episode, the small number of patients included, and the brief duration of monitoring (generally 24-48 hours). Detailed analysis of the beats initiating the event was not the focus of these studies.

With the advent of ICDs came the capability to register intracardiac electrograms during an arrhythmic event and to provide continuous monitoring. As a result, additional studies have been published, some of which focus on the initiation of the tachycardia. In 1994, Roelke et al. published an analysis of the initiation of 73 episodes of VT recorded in 22 patients with ICMP. In 45% of the episodes, a single PVC initiated the tachycardia, in 22% of the episodes, it was initiated by a pair of PVCs, and in 33% of the episodes, multiple PVCs initiated the tachycardia. Analyzing the morphology of the beats initiating VT, they have found that, in 48% of the episodes, the morphology of the PVC was similar to the VT morphology, and in the remaining 52%, the PVC was dissimilar to the VT morphology. The mean coupling interval of premature depolarizations was 364ms (280 to 610). The mean ratio of the premature coupling interval to the immediately preceding cycle length was 0.56
where the ratio was 0.60 in the episodes initiated with PVCs of a similar morphology and 0.53 in the morphologically dissimilar.[80]

Saeed et al. described 268 episodes of monomorphic VT registered in 52 patients with predominantly ICMP. The beat initiating an episode of VT was classified as a PVC when it was morphologically different from the subsequent tachycardia, or when it was morphologically similar but the coupling interval was > 110% of the VT CL. The initiation of an episode of VT was classified as extra-systolic if it was initiated by a PVC (figure 1). If the beat initiating the tachycardia was morphologically similar to the tachycardia and its coupling interval was < 110% of the VT CL, then it was labeled as the first beat of the episode and the tachycardia was classified as having a sudden initiation (figure 2). If the initiating beat was a paced beat, the tachycardia was termed pacing-induced. Extra-systolic initiation, sudden initiation and pacing-induced initiation were observed in 66%, 28% and 6% of the episodes, respectively. Reproducibility of the initiation was high in patients with more than 1 episode. 88% of these patients had at least 2 events with the same initiation pattern. The authors proposed that the different patterns of initiation could be related to different mechanisms of VT. The extra-systolic pattern would probably be related to re-entrant VTs with a PVC causing a slowing of conduction and the unidirectional block required for a re-entrant rhythm. Sudden VTs could be associated with focal VTs or with a re-entrant circuit initiated by a PVC arising from a site close to the re-entry circuit. Alternatively, sudden VTs could be initiated by concealed decremental conduction of the sinus beat just before the VT.[81] Others studies analyzing intracardiac electrograms of the initiation of monomorphic VT reported similar results. [82, 83] A 2013 review paper showed that the predominant initiation pattern of monomorphic sustained VT is extra-systolic (or non-sudden). Its frequency varies between 59% and 73% in the available literature.[47]
There are several electrophysiological differences between sudden and non-sudden onset patterns. For the sudden onset VTs, the preceding sinus rate was faster, the VT cycle length (CL) was longer, and the patients’ LVEF tended to be higher. These studies, however, were limited by their small sample size.[47, 80-84] None of them were randomized trials.

In the only randomized trial to analyze the initiation of ventricular tachyarrhythmia (MADIT II), the authors limited their focus to ventricular fibrillation episodes in a study population of patients with ischemic cardiomyopathy.[85]

**RELATIONSHIP BETWEEN INITIATION AND MECHANISM:**

The EP study for assessment of the mechanism of VT is accurate but not feasible in large samples due to its invasiveness and cost. Moreover, a VT must be sustained and well-tolerated to allow for proper evaluation. Consequently, efforts have been made to infer the mechanism of VT using patterns of initiation as proposed by Seed et al.[81]. The rationale is based on the known mechanisms for initiation of re-entrant tachycardias.

The unidirectional block required for re-entry is usually caused by a premature depolarization that finds one limb of the tachycardia in its refractory period. The premature depolarization is more commonly a (PVC), but can be a premature atrial complex conducted or tracked by a pacemaker. This mechanism will manifest in a non-sudden initiation pattern since the beat initiating the tachycardia will most likely have a different morphology compared with the tachycardia itself (Figure 1). There are two exceptional circumstances in which a re-entrant ventricular tachycardia may have a sudden initiation: 1) concealed decremental conduction of the sinus beat just before the VT, setting up a re-entry circuit [86] and 2) a PVC originating from the exit point of the re-entry. By contrast, focal VTs tend
to have a sudden initiation because the CLs and morphologies from single sources tend to be stable.

**DISCUSSION:**

Sudden cardiac death due to ventricular tachyarrhythmia is an important cause of death in developed countries. After the implementation of primary prevention for patients with low left ventricular EF with ICDs, recurrent ICD shocks became a major problem.

Monomorphic VT in patients with CHF and reduced left ventricular EF, and especially in ICMP, had been considered to be secondary to re-entry in more than 90% of cases[51]. There is some evidence in the literature pointing to a larger proportion of focal tachycardias in these patients. [41, 55, 73, 74]

The pattern of initiation can, in theory, indicate the mechanism of VT. With the rational proposed by Saeed et al. [81], a sudden initiation would be associated with focal VT whereas non-sudden initiation would be associated with re-entrant VT. More studies are required to prove this association. The limited data available shows that a faster preceding sinus rate is more common in sudden initiation. That fact could indicate a higher adrenergic tone favouring focal arrhythmias. Sudden initiation is also associated with a longer VT CL and a higher LVEF.[47, 80-84] Due to its applicability to large samples, analysis of the pattern of initiation has the potential for substantial contributions to the current understanding of VT mechanisms in patients with cardiomyopathy.

The majority of patients with low left ventricular EF have VTs that are hemodynamically unstable, and therefore do not allow activation and entrainment mapping during the tachyarrhythmia.[68] When ablation is needed, it is based on substrate mapping in sinus rhythm, which consists of identifying areas of scar (low voltages areas) with
abnormal conduction (fractionated electrograms, late potentials) and ablating these areas.[31, 43-46] This approach is particularly used in patients with ICMP, based on the concept that more than 90% of VTs in these patients have a reentrant mechanism, where certain areas would represent slow conduction channels critical for the circuit. However, this principle does not take into consideration two possibilities: 1) patients can have areas of slow conduction and areas of conduction block which are not manifest in sinus rhythm, known as functional block; 2) patients with ICMP may also have focal VTs, therefore, activation mapping and pace-mapping would be required if the VT is hemodynamically tolerated.

The current approach to VT ablation reduces recurrent ICD shocks in patients with ischemic cardiomyopathy undergoing ICD implantation for secondary prevention.[33] In the recently published VANISH trial, despite of a reduction in the composite primary outcome of death, ventricular tachycardia storm or appropriate shock from an ICD in the ablation arm, patients still had a 37.9% rate of recurrent ICD shocks and a 24.2% rate of VT storm, reflecting the need for improvement in the current management.[35] Individualized understanding of the mechanism of the VT can help in selecting treatment strategies, and the ICD recording of the VT initiation pattern may be a valuable tool in this selection.

Currently available literature lacks precise and homogeneous definitions of sudden and non-sudden onset patterns. ICDs do not routinely store electrograms of VT initiation, therefore the episodes analyzed represent only a sample, where the sampling process could have numerous biases.

The foundational studies defining the mechanism of VT were done more than 30 years ago. At that time, class I antiarrhythmic agents were commonly used in patients with
severely depressed LVEF, beta-blockers and ACE inhibitors were not universally used, and the majority of the patients with ischemic cardiomyopathy were survivors of a non-reperfused ST elevation MI. Furthermore, primary prevention with ICDs and cardiac resynchronization therapy were not common practice, and overall mortality rates were significantly higher than they are currently. Extrapolation of this early data to current practice may be misleading. New studies are necessary to define the mechanism of tachyarrhythmias in the current era of patients with cardiomyopathy at risk of VT.

CONCLUSIONS:

Despite many advances in preventing SCD in patients with low LVEF, VT remains an important healthcare burden. The pathophysiology of VT is not completely understood, especially in patients with NICMP. The proportion of focal VTs in patients with heart failure is likely underestimated.

With current generation ICDs, the pattern of initiation of a VT is an easily available piece of information that may help to understand its mechanism. Studies are necessary to further address the relationship between the initiation and the mechanism of VT. Analysis of patterns of initiation in large samples is also necessary to understand the influence of initiation patterns on long-term outcomes such as mortality and ICD shocks.
**Figure 1:** Intracardiac electrogram of a VT recorded with a bi-ventricular defibrillator showing an example a VT with extrasystolic or non-sudden initiation. VT=Ventricular tachycardia EGM=electrogram; PVC=premature ventricular complex.

**Figure 2:** Intracardiac electrogram of a VT recorded with a bi-ventricular defibrillator showing an example a VT with sudden initiation. VT=Ventricular tachycardia EGM=electrogram.
CHAPTER II

Defining the Pattern of Initiation of Monomorphic Ventricular Tachycardia Using the Beat-to-Beat Intervals Recorded on Implantable Cardioverter Defibrillators from the RAFT Study: A Computer-Based Algorithm

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ABSTRACT

Arrhythmia onset pattern may have important implications on morbidity, recurrent implantable cardioverter defibrillator (ICD) shocks, and mortality, given the proposed correlation between initiation pattern and arrhythmia mechanism. Therefore, we developed and tested a computer-based algorithm to differentiate the pattern of initiation based on the beat-to-beat intervals of the ventricular tachycardia (VT) episodes in ICD recordings from the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT).

Intervals on intracardiac electrograms from ICDs were analyzed backwards starting from the marker of VT detection, comparing each interval with the average tachycardia cycle length. If the morphology of the beat initiating the VT was similar to the morphology of the VT itself, the episode was considered sudden. If the morphology of the beat initiating the VT was not similar to the morphology of the VT itself, the episode was considered non-sudden.

The capability of the algorithm to classify the pattern of initiation based only on the beat-to-beat intervals allows for the classification and analysis of large datasets to further investigate the clinical importance of classifying VT initiation. If analysis of the VT initiation proves to be of clinical value, this algorithm could potentially be integrated into ICD software, which would make it easily accessible and potentially helpful in clinical decision-making.
INTRODUCTION

The pattern of initiation of ventricular tachycardia (VT) is classified as non-sudden (or extra-systolic) when the VT is initiated by a premature ventricular contraction (PVC) morphologically different of from the VT itself. The VT initiation is classified as sudden, when the beat initiating the tachycardia morphologically is similar to the subsequent beats.[47, 80-83] These patterns are theoretically related to the mechanism of the VT (re-entrant and focal, respectively) [81, 87]. Defining the pattern of the initiation of the VT therefore requires a morphological analysis of the VT that can be performed using a VT tracing obtained via ECG (e.g. Holter) monitoring or via interrogation of tracings from an implantable cardioverter defibrillator (ICD). Holter monitor analysis is limited by the short registration time of the arrhythmia episodes, which results in the small datasets in most available studies. [75-79]. Conversely, current generation ICDs provide continuous monitoring and storage of the intracardiac electrogram (EGM) which allows for registration of almost all VT episodes. However, while the EGM of the VT is frequently available, the EGM of the initiation is often not stored in the device. For the majority of the episodes, only the beat-to-beat intervals are registered for the first VT beats and the beats preceding arrhythmia detection (without EGM), which limits the study of the initiation pattern in large samples.

We developed and tested a computer-based algorithm to differentiate the pattern of initiation based on the beat-to-beat intervals of the VT episodes in ICD recordings from the RAFT study[88]. This tool can be used to analyse large databases with information about arrhythmia initiation, allowing further understanding of the arrhythmia and possibly revealing information regarding its mechanisms.
HISTORY OF THE DEVELOPMENT

The RAFT study included 1800 patients with mild-to-moderate heart failure symptoms, left ventricular ejection fraction (LVEF) ≤ 30%, and QRS duration ≥ 120 milliseconds. These patients were randomized into two equally sized groups. The control group received ICD plus optimal medical therapy, and the experimental group received a device with cardiac resynchronisation therapy (CRT) capability, as well as an ICD.[88]

The study represents a unique dataset that allows for the evaluation of events immediately preceding appropriate therapy for ventricular tachyarrhythmias. The data itself contains inter-beat intervals of ventricular and, where available, atrial events detected by the ICD. There are 5413 recorded episodes representing single or multiple VT events preceded by approximately 20 seconds of pre-tachycardia activity. Intracardiac EGMs are also available on an online platform (WebEGM), however the tachycardia initiation tracings were available for only 352 episodes. In the majority of the episodes, the device only registered the EGMs after the initiation of the VT (Figure 1). Previously described methodologies[80-83] compared the morphology of the first (i.e. initiating) beat with the morphology of the tachycardia; this type of analysis would be applicable to less than 10% of the sample. The presented computer-based algorithm allows for classification of the VT episodes based on the initiation pattern intervals alone, which are more often available. (Figure 1)

DESCRIPTION

The aim of the current study is to classify the pattern of initiation of VT episodes from the RAFT dataset based only on the initial beat-to-beat intervals. To achieve this goal two important steps were taken:
1 – The development of a computer based algorithm able to analyze the intervals and classify the initiation.

2 - The validation of this algorithm testing its accuracy on the episodes in which the tracings of the initiation were recorded.

The database: The intervals are formatted as text files comprised of comma-separated values. Each atrial or ventricular event detected by either type of device is stored as a single row that contains the serial code of the patient, the ICD model, the date of the episode, and additional event information depending on the type of device.

The algorithm: The data extraction software was developed using Java language, allowing for the interpretation of the interval data that can be plotted over time. The visual presentation of the data is similar to the dot-plot graphic displayed on the ICDs. This plot is part of a user interface that allows the user to flag episodes with markers for the baseline rhythm (regular paced, regular spontaneous, regular with ectopics), type of onset suspected (sudden vs. non-sudden), sinus cycle length (CL), tachycardia cycle lengths, as well as type and efficacy of therapies (Figure 2).

Starting from the marker of VT detection on the recording, the intervals were analyzed backwards, comparing each interval with the average tachycardia cycle length (CL). When the interval differed from the average tachycardia CL by a determined threshold (threshold 1), the algorithm classified the interval as the coupling interval of the first beat of the tachycardia. After determining the coupling interval of first beat of the tachycardia, the algorithm analyzed and compared the preceding interval with the average baseline CL, which is manually selected on the software. If the preceding interval matches the baseline
CL within a limit of variation (threshold 2) the tachycardia is considered sudden. If the preceding interval is different the baseline CL, the tachycardia is considered non-sudden.

As demonstrated in two examples (figure 3), the VT can have beat-to-beat variability. Thus, a threshold is required to distinguish the beat-to-beat variability of the VT from the abrupt change in the coupling interval when seen in the first beat of a VT.

Since the algorithm needs a baseline regular rhythm for comparison, episodes in which a baseline regular rhythm was not discernible were excluded (e.g. atrial fibrillation, PVCs which limit determination of a baseline rhythm, recordings already starting VT). If an abrupt change in the coupling interval was found in the middle of the tachycardia, the algorithm ignored it, as the changes can be related to fusion beats and capture beats.

A validation process was performed to determine the best values for the above-mentioned thresholds, and to test the accuracy of the algorithm. The 352 previously described WebEGM episodes were manually classified as sudden or non-sudden using available intracardiac tracings of the VT initiation. The criteria used was previously described by Saeed et al. [7] In short, if the morphology of the beat initiating the VT was similar to the morphology of the VT itself, the episode was considered sudden. If the morphology of the beat initiating the VT was not similar to the morphology of the VT itself, the episode was considered non-sudden. Given the requirement of a baseline discernible regular rhythm, there were 256 classifiable episodes (of 352 episodes).

After the classification, the episodes were randomly divided into two subsets. The first subset was used to test different thresholds and identify the most accurate. A receiver operator curve (ROC) was obtained using the manual classification as the gold standard. More than ten thousand pairs of thresholds were tested and plotted in the ROC defining the
most accurate value for each threshold (Figure 4). The second subset was used to test the thresholds found to be the most accurate in the first subset and validate them in a different sample.

In the first subset, the most accurate threshold (82.6% accuracy) was found using 18% of the tachycardia CL and 51 ms for threshold 1, and 12% of the sinus CL for threshold 2. Testing these thresholds in the second subset yielded an accuracy of 81.3%.

**CLINICAL ROLE**

Arrhythmia onset pattern may have important implications on morbidity, recurrent ICD shocks, and mortality, given the proposed correlation between initiation pattern and arrhythmia mechanism. [81, 87] However, this has never been properly studied, in part because the classification of the initiation pattern depended on the availability of the tracing when the arrhythmia initiates. In the RAFT study, the VT initiation tracings were available for less than 10% of the episodes. The capability of the algorithm to classify the initiation pattern based only on the beat-to-beat intervals allows for the classification and analysis of large datasets. If analysis of the VT initiation proves to be of clinical value, this algorithm could potentially be integrated into ICD software, which would make it easily accessible and potentially helpful in clinical decision-making.

The association between pattern of initiation and mechanism of VT has been postulated but not proven. Ischemic cardiomyopathy is known to be associated with re-entry as a mechanism for VT, and re-entry is more likely to be terminated by anti-tachycardia pacing.[51] The analysis of these datasets can be used to investigate whether VT initiation differs among patients with ischemic and non-ischemic cardiomyopathy and its relationship with response to anti-tachycardia pacing. Other applications for a tool to
classify VT initiation patterns include research to further understand if it has a role in
determining antiarrhythmic therapy, electrophysiologic testing, response to antiarrhythmic
therapy, recurrence of VT, and adverse prognosis. These proposed future research studies
can be conducted with databases similar to the RAFT study which also contains information
on recurrence of ventricular arrhythmias, adverse cardiovascular outcomes, and response to
antiarrhythmic medications.

CURRENT PROBLEMS

The 256 tracings used for the validation process represent a sample of episodes with
a discernible baseline regular rhythm and in which initiation tracings were recorded. A
device may register of the initiation if a function that records the pre-detection EGM was
enabled, or the device could be recording a prior event (e.g. a non-sustained VT) with
continuous registration until the initiation of sustained VT. Therefore, selection bias may
exist in the tracings used for the validation sample.

For several episodes, although the tracing of the initiation was registered, a far-field
EGM was not available, limiting the analysis of the morphology.

The accuracy of the algorithm was limited, although consistent between the two
subsets.

FUTURE DEVELOPMENTS

More recent devices are able to record the initiation of VT in all episodes.
Furthermore, the devices are able to record three channels during the VT, hence a far-field
EGM is always registered. These advances in technology can overcome the limitation of the
biased sampling and morphology analysis when only a nearfield EGM is available, possibly
resulting in more accurate threshold calculations.
CONCLUSION

A computer-based algorithm was developed and tested to classify the pattern of the VT initiation based only on the beat-to-beat intervals. This methodology can be applied to analysis of large datasets, potentially providing valuable information regarding the pattern of initiation of the VT and its clinical implications.
Figure 1: example of a VT episode recorded by dual chamber ICD. For the first VT beats only the marker intervals are available.
Figure 2: Example of an VT episode displayed in the computer software. The software displays two graphics in which the y axis represents the coupling interval and the x axis represents the time. On the upper graphic, ventricular couplings intervals are shown. Beginning of the recording shows a brief period of bi-ventricular pacing (BVP), followed by a period of red dots which represent sensed ventricular events. After the VT detection (VTD) an anti-tachycardia pacing is delivered, showed as black dots, leading to a brief termination with a period BVP. The tachycardia restarts and after two more attempts of anti-tachycardia pacing without termination of the tachycardia, a shock was delivered at the end of the graphic. CE stands for charge ended and VCD stands for ventricular charge delivered. On the lower graphic, the atrial coupling intervals are represented. Red dots represent sensed events, yellow dots represents sensing events on the post ventricular atrial refractory period, white dots represents atrial sensed events on the post ventricular atrial blanking period (ASPVABP) and the black dots represents atrial paced events.
Figure 3: A: Atrial EGM in blue and ventricular nearfield EGM in red. Episode of VT with sudden initiation. The coupling interval of the beat preceding the first beat of VT matches the average sinus CL. B: Ventricular near field EGM in blue and ventricular far-filed EGM in red. Example of VT with non-sudden initiation. The coupling interval of the beat preceding the first beat of VT does not match the average sinus CL. Note that the morphology of the beat initiating the VT is different of the VT itself, better evidenced on the far field EGM.
Figure 4: Receive Operator Curve (ROC) testing different pairs of thresholds using the manual classification as the gold standard. True positive are the sudden episodes classified as sudden, false positive are the sudden episodes classified as non-sudden.
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