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RECURRENT SYNCOPE EPISODES IN A MIDDLE-AGE WOMAN WITH HYPERTROPHIC CARDIOMYOPATHY: A CASE REPORT

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Abstract:

Macrolides are identified as a potential source of drug-induced arrhythmias in susceptible patients such as females, electrolyte alterations, and those with underlying prolonged QT interval. However, we usually find provocative agents or risk factors rather than main causes of arrhythmias. Herein, a 40 year-old woman with history of HCM who had undergone ICD implantation 18 months ago presented with malaise, low-grade fever, and non-productive cough. After her admission, three episodes of syncope occurred at rest. Interrogation of ICD revealed that ventricular tachycardia was responsible for loss of consciousness. Although appropriate ICD shocks disrupted the arrhythmia, these episodes stopped only after cessation of Levofloxacin. We reviewed ECG strips, which confirmed prolongation of QT intervals with a decreasing trend by elimination of Levofloxacin. In conclusion, we should observe small details and changes in clinical history as well as Para clinical data of the patient. Adverse effects of medications should be addressed in clinically relevant cases.

Key words: Drug interaction, Macrolides, ECG, QT interval, ICD, Arrhythmia

Abbreviations and acronyms:

HCM : Hypertrophic Cardiomyopathy, **ICD**: Implantable Cardioverter Defibrillator, **IE** : infective endocarditis, **MDI** : Metered dose inhaler, **ASH** : Asymmetric septal hypertrophy, **SAM** : systolic anterior motion, **LV** : Left Ventricle, **LVOT** : Left Ventricle outflow tract, **PAP** : Pulmonary artery pressure, **ECG** : Electrocardiogram, **bpm** : beats per minutes. **AMVL**: Anterior Mitral Valve Leaflets, **VT**: Ventricular tachycardia, **SVT**: Supraventricular tachycardia, **MYBPC3**: myosin-binding protein-C, **TdP** : torsade de pointes, **MYH**: Myosin Heavy chain, **FDA**: Food and Drug Administration , **FAERS** :FDA Adverse Events Reporting System , **LQTS**: Long QT syndrome

Case presentation

A 40-year-old woman, who was a known case of Hypertrophic Cardiomyopathy (HCM) and Hypertension since 3 years ago presented with transient attacks of declined consciousness to the emergency department of our hospital. Implantation of an ICD (Implantable Cardioverter Defibrillator) had been performed about 18 months ago due to non-sustained ventricular tachycardia manifested via dizziness episodes confirmed with 24-hour electrocardiographic Holter monitoring. She complained of three syncopal episodes both of which occurred at rest during 5 days preceding her last hospital admission. Initial symptoms were palpitation, malaise, low-grade fever, non-productive cough, and lightheadedness leading to her first hospitalization. Residual confusion (post-ictal state), unilateral weakness, blurred vision or headache were not reported. She did not mention any kind of chest discomfort. However, she had experienced longstanding dyspnea on exertion without recent exacerbation.

Initial evaluations were performed surrounding probable differential diagnosis of malaise, and low-grade fever including infective endocarditis (IE) and viral/interstitial pneumonia in another medical center until last week. Ultimately, IE was ruled out with negative blood cultures and incompatible echocardiographic features in addition to cessation of fever in the first 3 days of disease onset. Given her clinical picture as cough accompanied with low-grade fever and interstitial opacities on chest radiogram, she was treated with Levofloxacin 750 mg once daily with a diagnosis of community acquired pneumonia. Her other medications included furosemide (20 mg twice daily), Verapamil 40 mg twice daily, metoprolol 50 mg twice daily, Seroflo (MDI), and Ipratropium bromide (MDI). Then she felt three aforementioned episodes, which were concordant with probable diagnosis of cardiac syncope owing to

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associated palpitation, short duration, lack of neurologic signs and symptoms and incidence at sitting position. Her primary clinical assessment in the emergency department revealed stable hemodynamic status. Vital signs were as follows: blood pressure: 112/70, heart rate: 90 bpm, respiratory rate: 13/min and Temperature: 37.7 C^0. Jugular vein pressure was within normal range. Fine end- inspiratory crackles with simultaneous mild generalized wheezing were found in auscultation of the lungs. The point of maximal impulse appeared forceful, sustained and laterally displaced, accompanied with Bisferiens pulse and a prominent S4 gallop was present. We found a harsh, crescendo–decrescendo systolic murmur along the upper left sternal border increased following Valsalva maneuver. Further parts of physical examination were unremarkable. Previous Transesophagial echocardiography report had demonstrated features of HCM without considerable alteration compared to the time of ICD implantation. LV ejection fraction was 55 % with diastolic dysfunction of grade 2. Asymmetric septal hypertrophy (ASH) specified via increased diameters of interventricular septum and LV posterior wall (28 mm and 19 mm, respectively). Thick mitral valve with severe mitral regurgitation and underlying SAM (systolic anterior motion of AMVL), high LVOT gradients (mean PG: 39 mmHg), Moderate pulmonary hypertension (PAP: 50 mmHg), were also observed. Figures 1A and 1B display her ECG strips obtained two days after last syncopal episode during last admission. She experienced two consecutive similar episodes thereafter (early in first day of admission in our hospital) lasting about 2 minutes. All lab test measurements were within normal range particularly serum electrolytes including potassium: 4.1 , Ca: 9.3, and Mg: 2.3. Figure 2 and Figure 3 depict the result of ICD interrogation providing VT episodes terminated via appropriated shock.

Discussion

Although the longstanding debate concerning the net benefit of ICD implantation in HCM continues, tailored case selection may guarantee the patients advantage. In this regard, a recent systematic review have underscored the low rate of appropriate intervention about 4.8% per annum [1]. However, the present patient had received multiple appropriate ICD shock therapies secondary to ventricular tachycardia episodes. Herein, tachyarrhythmias (such as VT or SVT) leading to ICD shock in relation with recent medications and acquired long QT interval or probable underlying electrolyte disorders were at the top of the list for etiologic factors. Mainstay of the stepwise diagnostic approach should be stringent history taking. Thus, we investigated for culprit drugs, which the patient had used during her last admission. Since there were no considerable electrolyte, derangement at symptomatic intervals and ECG showed prolonged QT interval we focused on her recent drugs .Tavanex (Levofloxacin) and salmetrol-fluticasone inhaler were two potential suspects but the former was prescribed recently in the preceding admission. As the device analysis revealed true detection and termination of polymorphic ventricular tachycardia episodes coinciding with syncope attacks confirmed the diagnosis. Nevertheless, a wide variety of factors might serve as triggers of VT in HCM patients. Variable grades of hypertrophy, focal fibrosis, and dynamic obstruction of left ventricular outflow have been delineated in these patients [2]. Given this fact, cessation of the symptoms as well as recurrent arrhythmias occurred after we stopped levofloxacin. In the same way, QT interval gradually declined over the corresponding timeline. A substantial issue is driven by polypharmacy including widespread use of common antibiotics particularly quinolones. Researchers have described various genotypes as correlates of long QT among which MYBPC3 encoded Myosin binding protein C3 and MYH7 are notable [3].

One of the best known and most important etiologic factors of QT interval prolongation and resultant Torsade de Pointes (TdP) is drug induced QT prolongation [4]. A 2010 study using FDA Adverse Events Reporting System (FAERS) identified macrolides, fluoroquinolones and linezolide as TdP inducing agents [5]. A recent study using the same database has shown similar results. The widespread use of the fluoroquinolones has raised the question of the cardiac safety of these medications, which is actually more favorable than many other drug classes [6]. Analyzing the same FAERS database has showed a more favorable safety profile with fluoroquinolones than many other antibiotics. The QT prolonging effect of fluoroquinolones is a result of their interference with a potassium channel on cardiac cell membranes. QT prolongation is a class effect of fluoroquinolones but different drugs of the class have varying degrees of prolongation “power”. There is overwhelming evidence that moxifloxacin has the greatest effect on QT interval and ciprofloxacin is the weakest of fluoroquinolones when it comes to prolonging QT, all other drugs lie somewhere in between this spectrum. Despite all these, it must be noted that the overall risk of QT prolongation with fluoroquinolones is nonetheless small and TdP with these drugs in absence of other risk factors is rare. Caution is advised when it comes to prescribing fluoroquinolones (or any other antibiotic with QT prolonging effects for that matter) in patients who have other risk factors for TdP such as electrolyte imbalance, congenital QT prolongation syndromes and those who take other drugs which can prolong QT (such as Class IC antiarrhythmic agents like quinidine, procainamide and amiodarone)[4]. In fact, one study has showed that in the case of

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ciprofloxacin and levofloxacin it is the concurrent drugs or other clinical risk factors that cause arrhythmia. Thus, controversy remains surrounding major culprit or the principal cause of dysrrythmia.[5] Although, it must be noted that most clinical trials evaluating proarrhythmic effects of fluoroquinolones have had fairly small sample sizes, thus interpreting their results must be done with ultimate caution.

Our findings have important clinical implications. Routine QTc assessment should be performed in patients with HCM, particularly in those for whom the concomitant use of medications with a known QT-prolonging effect is intended. The use of QT-prolonging drugs should be weighed against potential risks, and the QT interval monitored regularly during treatment. Furthermore, these patients should be adequately counseled with regard to potential interaction with other QT-prolonging drugs (antibiotics, etc.) and of common electrolyte disturbances. One other issue, which must be discussed regarding our patient, is the possibility of a latent form of Long QT Syndrome (LQTS) or a "form fruste" type. These patients test positive for the genetic mutation responsible for LQTS yet on their surface electrocardiogram, the QT interval is only borderline prolonged or in some cases, it might be even normal[9]. Although rare but individuals with these condition are at increased risk of TdP and it is only after multiple syncope attacks and extensive and lengthy workups that the patient's condition is "incidentally" discovered. Electrocardiographic monitoring of high-risk patients such as those who take drugs, which makes them prone to adverse arrhythmogenic effects of antibiotics, and those with known structural heart diseases, known syndromes of Long QT Interval and history of renal impairment and electrolyte imbalance might be a logical next step in order to avoid catastrophic situations.

References:

1. Wang N, Xie A, Tjahjono R, et al. Implantable cardioverter defibrillator therapy in hypertrophic cardiomyopathy: an updated systematic review and meta-analysis of outcomes and complications. *Ann Cardiothorac Surg*. 2017;6(4):298–306. doi:10.21037/acs.2017.07.05.
2. Johnson JN, Grifoni C, Bos JM, et al. Prevalence and clinical correlates of QT prolongation in patients with hypertrophic cardiomyopathy. *Eur Heart J*. 2011;32(9):1114–20. doi:10.1093/eurheartj/ehr021.
3. Jouven X, Hagege A, Charron P, et al. Relation between QT duration and maximal wall thickness in familial hypertrophic cardiomyopathy.Heart2002; 88:153 – 157.
4. Roden DM. Clinical Practice. Long QT Syndrome. N Engl J Med. 2008;358:169-76
5. Poluzzi E, Raschi E, Motola D, Moretti U, De Ponti F. Antimicrobials and the risk of torsades de pointes: the contribution from data mining of the US FDA Adverse Event Reporting System. Drug Saf 2010;33:303-14.
6. Teng, C., et al. (2019). "Torsades de pointes and QT prolongation Associations with Antibiotics: A Pharmacovigilance Study of the FDA Adverse Event Reporting System." Int J Med Sci 16(7): 1018-1022.
7. Niedrig, D., et al. (2016). "Drug safety of macrolide and quinolone antibiotics in a tertiary care hospital: administration of interacting co-medication and QT prolongation." Eur J Clin Pharmacol 72(7): 859-867.
8. Makaryus A et al. Effect of Ciprofloxacin and Levofloxacin on the QT Interval. Southern Medical Journal. 99;1:52-56
9. Guthlin M et al. Form Fruste of Long QT Syndrome. Z Kardiol. 1996 Jan;85(1):53-8 (Article in German)

Declarations:

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Contributions: AB and SG provided the core concept of the case report and performed treatment of the patient as well as supervising the study. ZH and A.A collected the data. All authors participated in writing the draft of the manuscript. AB revised the final proof of the manuscript before submission. SA.S and MM prepared the figures. All authors read and approved the final manuscript.

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Availability of data and material: Not applicable to this type of study.

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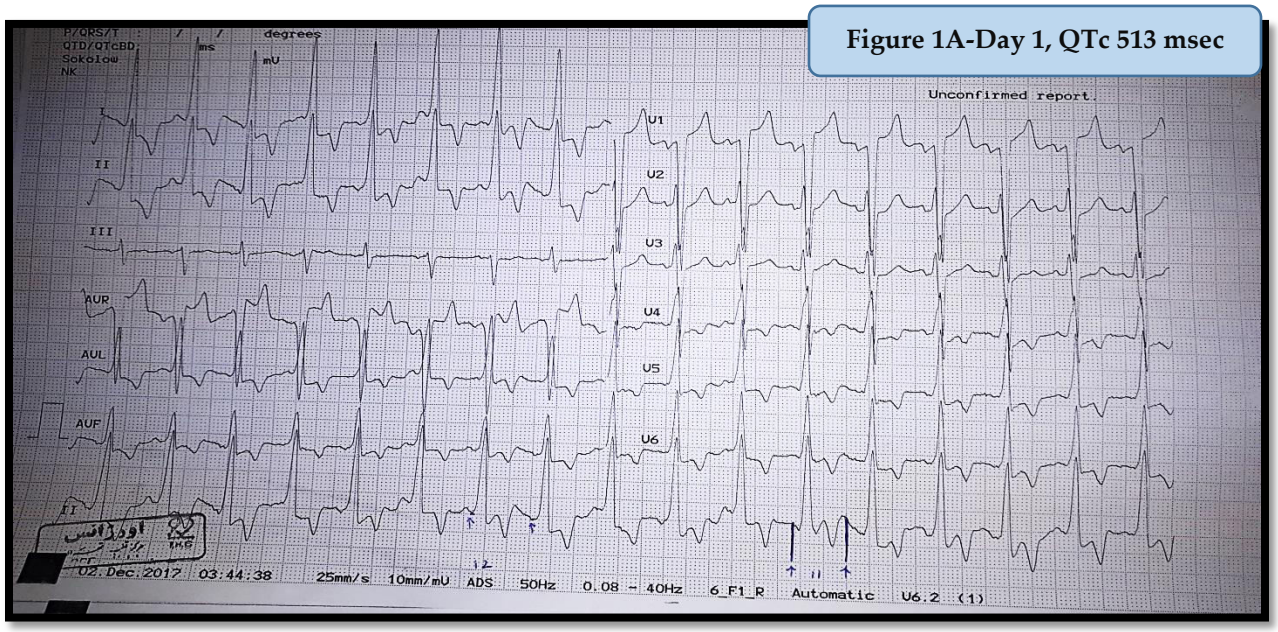


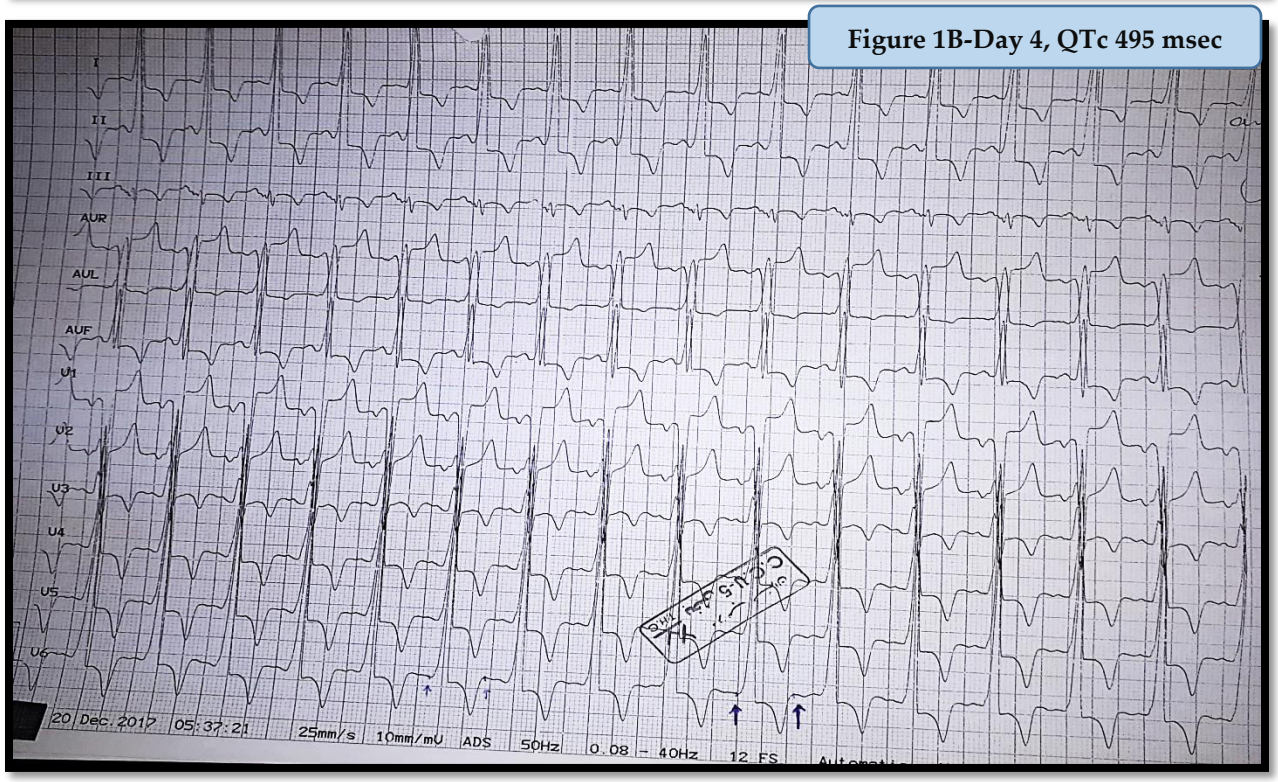
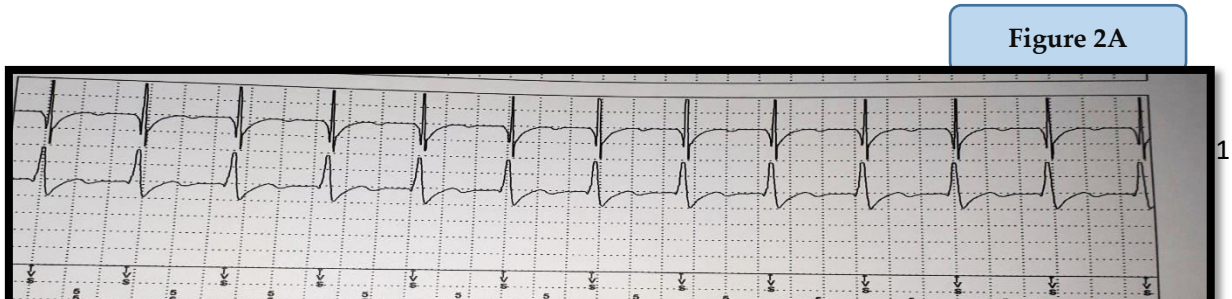


Figure 1A-B. Initial and subsequent ECG strips of the patient. **Figure 1A** shows baseline electrocardiogram obtained in first day of admission. Normal sinus rhythm, normal axis, LVH criteria, secondary ST depression and T wave inversion in leads I, AVL, II, III, AVF, V4-V6. Prolonged QT interval, which is approximately 513 msec. **Figure 1B,** illustrates ECG of the patient recorded in day 4 early after cessation of Levofloxacin. Corrected QT interval declined to approximately 495 msec.



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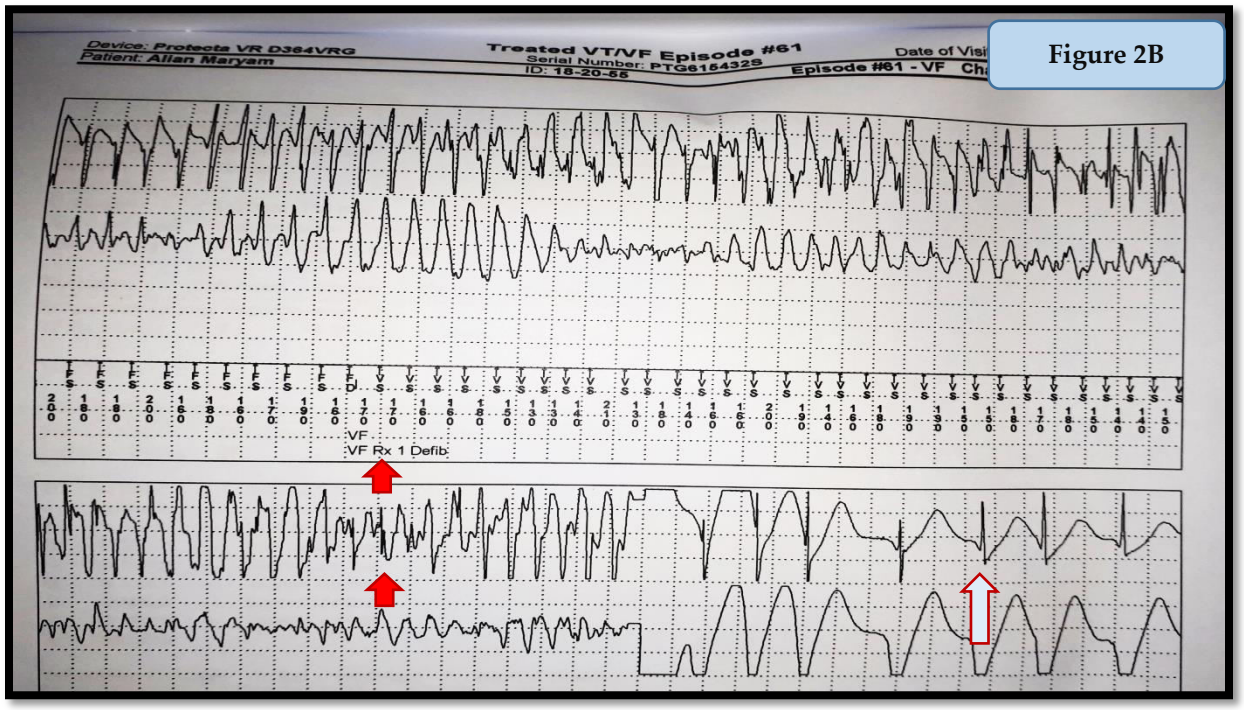

Figure 2A-B. Two episodes of polymorphic VT runs detected via ICD. **Figure 2A** shows baseline electrocardiogram obtained from atrial and ventricular channels. Normal innate rhythm sensed by ICD in upper part. In the lower part (mid of the lower row indicated via arrow) a premature ventricular beat as R on T wave initiates VT. **Figure 2B,** this figure depicts another episode of polymorphic VT detected by ICD. Appropriate defibrillation was delivered via ICD (red arrow) and arrhythmia was terminated. Blue arrow shows temporary post-defibrillation pacing for seconds prior to restoration of innate normal sinus rhythm.

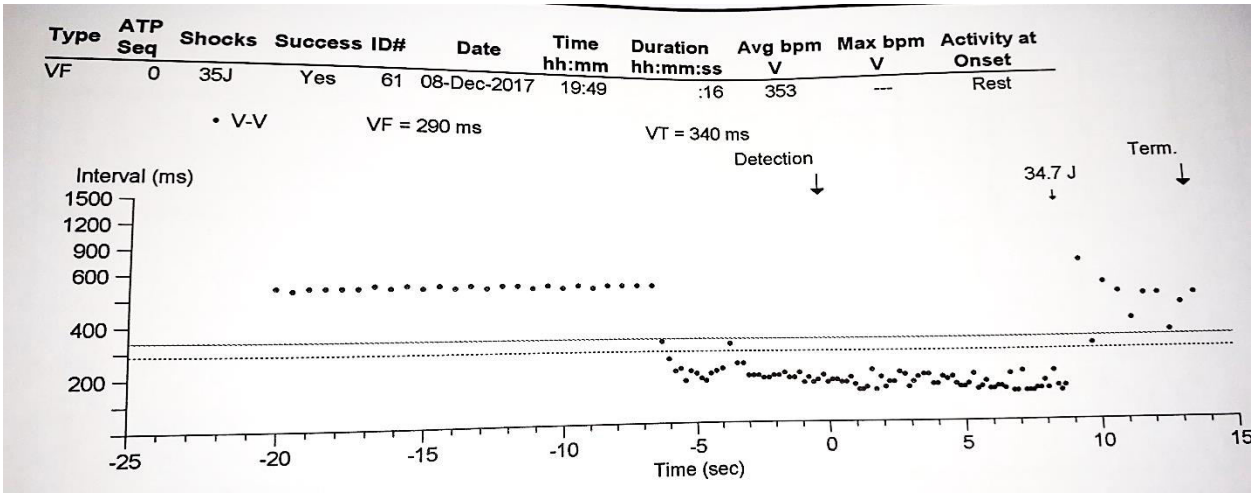

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Figure 3. This montage illustrate a graph showing one of the VT episodes diagnosed and treated via ICD. Vertical axis shows interval of two beats (V-V) in msec. The threshold for detection of VT and VF was defined as intervals lower than 340 msec and 290 msec, respectively. These values correspond to 180 bpm and 210 bpm, respectively. Following detection of tachyarrhythmia (dots below the threshold lines), a shock with power of 34.7 J was delivered and normal rhythm was restored (dots above the horizontal lines).