RR interval variability in the evaluation of ventricular tachycardia and effects of implantable cardioverter defibrillator therapy

Keita Tsukahara[1], Yasushi Oginosawa[2], Yoshihisa Fujino[3], Toshinobu Honda[4], Kan Kikuchi[5], Masatsugu Nozoe[6], Takayuki Uchida[7], Hitoshi Minamiguchi[8], Koichiro Sonoda[9], Masahiro Ogawa[10], Takeshi Ideguchi[11], Yoshihisa Kizaki[12], Toshihiro Nakamura[13], Kageyuki Oba[14], Satoshi Higa[15], Keiki Yoshida[16], Keishiro Yagyu[1], Taro Miyamoto[1], Yamagishi Yasunobu[17], Hisaharu Ohe[1], Ritsuko Kohno[18], Yutaka Otsuji[3], and Haruhiko Abe[19]

[1]University of Occupational and Environmental Health Japan
[2]Sangyo Ika Daigaku
[3]University of Occupational and Environmental Health, Japan,
[4]Kumamoto Junkanki Hospital
[5]Japan Community Healthcare Organization, Kyushu Hospital
[6]Saiseikai Fukuoka General Hospital
[7]Iizuka Hospital
[8]Osaka University Graduate School of Medicine
[9]Sasebo City General Hospital
[10]Fukuoka University
[11]University of Miyazaki
[12]Hakujujikai Sasebo Chuo Hospital
[13]National Hospital Organisation Kyushu Medical Center
[14]Yuai Medical Center
[15]University of the Ryukyus
[16]Saga-ken Medical Centre Koseikan
[17]University of Occupational and Environmental Health Hospital
[18]University of Occupational and Environmental Health, Kitakyushu, Japan
[19]University of Occupational and Environmental Health, Japan

December 27, 2020

Abstract

Introduction: An implantable cardioverter defibrillator (ICD) is the most reliable therapeutic device for preventing sudden cardiac death in patients with sustained ventricular tachycardia (VT). Regarding the effectiveness of the ICD, targeted VT is defined based on the tachyarrhythmia cycle length. However, variation of the RR interval variability of VTs does occur. A few studies reported on VT characteristics and effects of ICD therapy according to RR interval variability. This study aimed to identify the clinical characteristics of VTs and effects of ICD therapy according to RR interval variability. Methods: We analyzed 821 VT episodes in 69 of 185 patients treated with ICDs or cardiac resynchronization therapy defibrillators. VTs were classified as regular or irregular based on RR interval variability. We evaluated successful termination using anti-tachycardia pacing (ATP)/shock therapy, spontaneous termination, and acceleration between regular and irregular VTs. Reproducibility of the

RR interval variability in one VT episode and within an individual with recurrent VT episodes was evaluated. Results: Regular VT was significantly more successfully terminated than irregular VT by ATP therapy. There was no significant difference in shock therapy or VT acceleration, irrespective of the variability of the VT cycle length. Spontaneous termination of VT occurred significantly more often in irregular than in regular VT. Reproducibility of RR interval variability in an episode and individual was 89% and 73%, respectively. Conclusion: ATP therapy showed greater effectiveness for regular than for irregular VT. Spontaneous termination was more common in irregular than in regular VT. RR interval variability of VTs is reproducible.

RR interval variability in the evaluation of ventricular tachycardia and effects of implantable cardioverter defibrillator therapy

Keita Tsukahara MD[a], Yasushi Oginosawa MD[a], Yoshihisa Fujino MD[b], Toshihiro Honda MD[c], Kan Kikuchi MD[d], Masatsugu Nozoe MD[e], Takayuki Uchida MD[f], Hitoshi Minamiguchi, MD[g], Koichiro Sonoda MD[h], Masahiro Ogawa MD[i], Takeshi Ideguchi MD[j], Yoshihisa Kizaki MD[k], Toshihiro Nakamura MD[l], Kageyuki Oba, MD[m], Satoshi Higa, MD[n], Keiki Yoshida MD[o], Yagyu Keishiro MD[a], Taro Miyamoto MD[a], Yasunobu Yamagishi MD[a], Hisaharu Ohe MD[a], Ritsuko Kohno MD[c], Yutaka Otsuji MD[a], Haruhiko Abe MD[p]

[a]The Second Department of Internal Medicine, University of Occupational and Environment Health, Japan, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu 807-8555, Japan

[b]The Department of Environmental Epidemiology Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health, Japan, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu 807-8555, Japan

[c]Division of Cardiology, Kumamoto Junkankika Hospital, 2-15 Miyukifueda, Minami-ku, Kumamoto 861-4172, Japan

[d]Division of Cardiology, Japan Community Healthcare Organization, Kyushu Hospital, 1-8 Kishinoura, Yahatanishi-ku, Kitakyusyu 806-8501, Japan

[e]Division of Cardiology, Saiseikai Fukuoka General Hospital, 1-3 Tenjin, Cyuou-ku, Fukuoka 810-0001, Japan

[f]Department of Cardiovascular Surgery, Iizuka Hospital, 3-83 Yoshiomachi, Iizuka 820-8505, Japan

[g]Department of Cardiology, Osaka Police Hospital, 10-31 Kitayamacyo, Tennoji-ku, Osaka 543-0035, Japan

[h]Department of Cardiology, Sasebo City General Hospital, 9-3 Hirasecyo, Sasebo 857-8511, Japan

[i]Department of Cardiology, Fukuoka University School of Medicine, 7-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan

[j]Department of Internal Medicine, Circulatory and Body Fluid Regulation, Faculty of Medicine, University of Miyazaki, 5200 Kiyotakechokihara, Miyazaki 889-1601, Japan

[k]Department of Cardiology, Sasebo Chuo Hospital, 15 Yamatocho, Sasebo, Nagasaki 857-1165, Japan

[l]Department of Cardiology, National Hospital Organization Kyushu Medical Center, 1-8-1 Jigyohama, Chuo-ku, Fukuoka 810-8563, Japan

[m]Department of Cardiology, Yuai Medical Center, 50 Yone, Tomigusuku, Okinawa 901-0224, Japan

[n]Cardiac Electrophysiology and Pacing Laboratory, Division of Cardiovascular Medicine, Makiminato Central Hospital, Okinawa, 1199 Makiminato, Urasoe, Okinawa 901-2131, Japan

[o]Department of Cardiology, Saga-ken Medical Centre Koseikan, 400 Kasemachinakabaru, Saga 840-0861, Japan

[p]Department of Heart Rhythm Management, University of Occupational and Environment Health, Japan, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyusyu 807-8555, Japan

DISCLOSURES

Data availability statement: The study data is available upon request.

Funding Sources statement: This research was supported by a grant from Medtronic Japan.

Conflict of interest disclosure : This study was financially supported by Medtronic Japan. Dr. Satoshi Higa is a consultant to Japan Life Line and Johnson & Johnson and received ' 'speaker's honoraria from Japan Life Line, Medtronic, Abbott, Bayer, Biotronik, Boehringer-Ingelheim, Bristol-Myers, Daiichi-Sankyo Pharmaceutical Company, and Pfizer.

Ethics approval statement: The study protocol was approved by the institutional review board of each participating center.

Patient consent statement: Written informed consent was obtained from the patients for obtaining the data.

Permission to reproduce material from other sources: N/A

Clinical trial registration : N/A

Address for correspondence: Yasushi Oginosawa MD, PhD.

The Second Department of Internal Medicine, University of Occupational and Environment Health, Japan, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyusyu 807-8556, Japan

Tel.: +81-93-691-7250, Fax: +93-691-6913

E-mail: y-ogi@med.uoeh-u.ac.jp

ORCID: http://orcid.org/0000-0002-0955-7791

Abstract

Introduction: An implantable cardioverter defibrillator (ICD) is the most reliable therapeutic device for preventing sudden cardiac death in patients with sustained ventricular tachycardia (VT). Regarding the effectiveness of the ICD, targeted VT is defined based on the tachyarrhythmia cycle length. However, variation of the RR interval variability of VTs does occur. A few studies reported on VT characteristics and effects of ICD therapy according to RR interval variability. This study aimed to identify the clinical characteristics of VTs and effects of ICD therapy according to RR interval variability.

Methods: We analyzed 821 VT episodes in 69 of 185 patients treated with ICDs or cardiac resynchronization therapy defibrillators. VTs were classified as regular or irregular based on RR interval variability. We evaluated successful termination using anti-tachycardia pacing (ATP)/shock therapy, spontaneous termination, and acceleration between regular and irregular VTs. Reproducibility of the RR interval variability in one VT episode and within an individual with recurrent VT episodes was evaluated.

Results: Regular VT was significantly more successfully terminated than irregular VT by ATP therapy. There was no significant difference in shock therapy or VT acceleration, irrespective of the variability of the VT cycle length. Spontaneous termination of VT occurred significantly more often in irregular than in regular VT. Reproducibility of RR interval variability in an episode and individual was 89% and 73%, respectively.

Conclusion: ATP therapy showed greater effectiveness for regular than for irregular VT. Spontaneous termination was more common in irregular than in regular VT. RR interval variability of VTs is reproducible.

Keywords: ventricular tachycardia, implantable cardioverter defibrillator, RR interval variability, shock therapy, anti-tachycardia pacing therapy

1 INTRODUCTION

An implantable cardioverter defibrillator (ICD) is currently the most reliable therapy for preventing sudden death in patients with sustained ventricular tachycardia (VT) associated with organic heart disease.[1-4] ICDs can terminate life-threatening VTs by using electrical shocks, or anti-tachycardia pacing (ATP), or

both. Recent studies have shown that electrical shocks for ventricular tachyarrhythmia may lead to a worse prognosis, such as mortality or morbidity.[5,6]Therefore, it is essential to reduce the use of shock therapy to terminate VT. Although the effectiveness of ATP therapy has been extensively reported, [7-9] it occasionally induces VT acceleration,[10,11] or progression to ventricular fibrillations (VFs). Many studies on the effectiveness of ICD therapy have reported that the cycle length defines VTs best targeted by ICD therapy. However, in addition to cycle length, the targeted VTs are characterized by RR interval variability (Figure 1A). Variation in the RR interval in tachyarrhythmia distinguishes VTs from supraventricular tachycardia, such as atrial fibrillation.[12] Concerning the RR interval variability in VT, there are few reports on the clinical characteristics of VT or the effectiveness of ATP therapy.

This study aimed to evaluate the relationship between RR interval variability in VTs and clinical characteristics of VT, including the effects of ICD therapy.

2 METHODS

The VTs per episode, recorded using an ICD or CRT-D device, were classified as regular or irregular VTs according to the RR interval variability of the cycle length. Based on this variability, we evaluated the rates of VT termination using ATP or shock therapy, and spontaneous termination, and acceleration. Additionally, the reproducibility of the RR interval variability of VTs (regular or irregular) in both an episode and an individual was evaluated.

2.1 Study design and population

This was a retrospective, multicenter, observational study. The study protocol was approved by the institutional review board of each participating center. The data analyzed were collected from 69 patients who experienced episodes of ventricular arrhythmias. They were among 185 patients involved in the Defibrillator with Enhanced Features and Settings for Reduction of Inaccurate Detection (DEFENSE) Trial.[13] Briefly, that study compared the SmartShock Technology (SST) algorithm with the conventional VT detection algorithms. The trial enrolled consecutive recipients of an ICD or cardiac resynchronization therapy defibrillator (CRT-D) that used the SST algorithm (Protecta XT ICD [DR, VR], Protecta XT CRT-D [DR], and Evera XT ICD [DR, VR]; Medtronic, Minneapolis, MN, USA). Patients whose device programming did not match the study requirements (Supplementary Table 1), or who were unable to complete two years of follow-up, or who were unable to provide informed consent were excluded from this research. The recipients were followed-up every 6 months for up to 2 years after device implantation, by remote monitoring of their device, or in the outpatient clinic. The devices were assessed at all scheduled and unscheduled follow-up visits. The DEFENSE trial revealed that, compared with the conventional algorithms, the SST discrimination algorithm significantly lowered the rate of inaccurate VT detection.

The VT episodes were evaluated as follows: of the 185 patients initially enrolled, 69 patients experienced 821 episodes of ventricular arrhythmias (VT, fast VT, or VF); of the 821 episodes, 608 (74%) were judged as true ventricular tachyarrhythmia, and 213 (26%) were judged as other episodes, including atrial fibrillation/atrial flutter (n = 26), sinus tachycardia or atrial tachycardia (AT) (n = 178), and T-wave oversensing (n = 9), leaving data from just 53 patients that exhibited true ventricular tachyarrhythmia. Each entire episode was reviewed by an independent adjudication committee to determine whether or not the diagnosis was appropriate.

2.2 Analysis of RR interval variability of VT

Of the 608 true VT/VF episodes mentioned above, only cycle lengths of [?]240 ms were considered as VT episodes in this study.

VT cycle length variability was determined based on a previous report; 10 RR intervals, from 2 seconds after the onset of VT on intracardiac electrograms, were obtained by automatic reading of the devices, with an accuracy of 10 ms.[12] VT was judged as irregular if any difference between two successive beats was > 20 ms at least once in 10 RR intervals; otherwise it was classified as regular.[12] When ATP was administered

more than once in an episode, evaluation of the RR interval variability after the first therapy session was performed using the 10 RR intervals occurring immediately before any subsequent ATP therapy.

2.2.1 VT termination

Episode termination was used to confirm the classification of success by ATP therapy. Termination occurring more than five beats after therapy was deemed unsuccessful and was classified as spontaneous termination after ATP delivery[10] Furthermore, VTs that terminated naturally without ATP or shock therapy were defined as spontaneous termination without therapy

2.2.2 VT Acceleration

Ventricular rhythm acceleration following ATP therapy was defined as a 10% decrease in cycle length.[10]

2.3 Reproducibility of RR interval variability of VT

We examined the reproducibility of RR interval variability of VT from two perspectives, firstly, reproducibility within an episode (RE), and secondly, reproducibility within an individual (RI).

RE was evaluated when there were two or more VTs in one episode (that is, ATP therapy was performed more than once in an episode). Of the VTs classified on the basis of RR interval variability within an episode, the ratio of the larger number of VTs by type (i.e., regular or irregular) was defined as RE (Figure 1B). If the numbers of regular and irregular VTs were identical in an episode, the episode was assigned according to the variability of the first recorded VT in the episode.

RI was assessed in patients with multiple VT episodes. The ratio of the larger number of VTs by type to the number of total VT episodes in all episodes within an individual was defined as RI (Figure 2).

2.4 Statistical analysis

Continuous data are presented as mean and standard deviation (SD). Univariate and multivariate odds ratios for VT termination and acceleration were estimated. A multilevel logistic regression was applied to estimate the odds ratios since VT episodes were nested within individuals. The multivariate model included RR interval variability of VTs (regular or irregular), average VT rate (beats per minute [bpm]), sex, ischemic cardiomyopathy, and use of an antiarrhythmic drug, β-blocker, angiotensin-converting enzyme inhibitor (ACE-I), or angiotensin II receptor blocker (ARB). Statistical analysis was performed using STATA version 16 (StataCorp LP, College Station, TX, USA). The level of statistical significance was set at $p < 0.05$.

3 RESULTS

3.1 Study groups

In a study group of 53 patients with an ICD or CRT-D, episodes with an unknown medication history (n = 77 in 7 patients), episodes with a cycle length < 240 ms (n = 8 in 7 patients), and episodes in which the starting point of ventricular tachyarrhythmia could not be confirmed on intracardiac electrocardiogram (n = 58 in 7 patients) were excluded; consequently, the remaining 465 episodes in 43 patients were included in the present analyses (Figure 3, Tables 1 and 2).

3.2 VT termination

Among the 465 episodes in 43 patients, 290 were managed with ATP therapy, 10 with shock therapy without ATP (shock therapy was administered after ATP therapy in 17), and 165 without therapy.

The characteristics of ATP therapy are summarized in Supplementary Table 2. The first pacing program for ATP therapy was set as burst pacing in all cases. ATP therapy terminated 85% of VT episodes (n = 246), and shock therapy terminated 100% of episodes (n = 27). After ATP delivery, the rate of spontaneous termination was 5% (n = 24), and the spontaneous termination rate without therapy was 31% (n = 145). VT termination could not be confirmed using intracardiac electrocardiography, i.e., episodes that were out of the VT zone without termination, in 5% of the episodes (n = 23).

In terms of ATP therapy, regular VTs showed significantly more successful terminations than irregular VTs ($p < 0.001$, odds ratio, 7.56). There was no significant difference in VT termination using ATP therapy between ischemic and non-ischemic cardiomyopathies. In addition, VT episodes with a faster rate showed a lower termination rate ($p = 0.002$, odds ratio, 0.97; Table 3). Spontaneous termination after ATP delivery occurred significantly more frequently in irregular than in regular VTs ($p < 0.001$, odds ratio, 30.58; Table 4). The VT rate had no significant effect on spontaneous termination after ATP delivery. For episodes in which no therapy was administered, spontaneous termination without therapy was more commonly observed in irregular than in regular VTs ($p = 0.001$, odds ratio, 6.06).

3.3 VT Acceleration

In 290 VT episodes of ATP therapies, occurrences of VT acceleration were significantly associated with faster than with slower VTs ($p = 0.006$, odds ratio, 1.04; average VT heart rate of episodes including acceleration vs. no acceleration, 200 bpm, SD: 21 vs. 178 bpm, SD: 25). In contrast, no significant difference was observed in acceleration occurrence in other items (Table 5).

3.4 Reproducibility of RR interval variability of VT

Overall, in 47 episodes in 14 patients, ATP therapy was administered more than once per episode. Of those, 30 episodes included a higher proportion of regular VTs (12 patients), and 17 episodes included a higher proportion of irregular VTs (8 patients). The reproducibility of VT variability within an episode was 89% with an SD of 19 (regular VT, 94%; SD, 15; irregular VT, 80%; SD, 21). Additionally, 27 patients had more than two VT episodes. The reproducibility of RR interval variability of VT in individuals was 73%, with an SD of 18 (ischemic vs. non-ischemic, 71%, SD: 17 vs. 75%, SD: 18).

4 DISCUSSION

Based on the variability of the VT cycle length, the three important findings of this study were as follows: first, ATP therapy produced a significantly higher termination rate in regular than irregular VTs. Second, spontaneous termination after ATP delivery or without therapy occurred significantly more frequently in irregular than in regular VT. Third, reproducibility of RR interval variability of VT was high, both per episode and per individual.

The mechanism and properties of tachycardia, substrate, local electrophysiology, and stimulation site affect the success of ATP attempts in terminating VTs.[14] While it may be difficult to capture all of this information in an ICD, focusing on RR interval variability may be important to improve ATP treatment effectiveness. Three types of VT mechanisms are known—reentry, triggered activity, and automaticity. In general, the regular heart rate is found in VT due to the reentry mechanism, and the irregular heart rate is a finding of non-reentrant VT.[15] According to previous reports, small changes in the VT cycle length suggested the increase in ATP effectiveness.[16] That evaluation used the percentage of variation, which was calculated by dividing the mean difference between each RR interval and the next one by the VT cycle length. Furthermore, ATP therapy is more effective for VTs that have smaller ventricular beat-to-beat morphologic variation on intracardiac recordings than for those that do not.[17] We evaluated the VT characteristics using a simple method, different from the one used in previous studies, to purely measure the variability of VT cycle length. In addition, ventricular tachyarrhythmia caused by a triggered activity or automaticity of the mechanism, can be difficult to terminate using programmed electrical stimulation with reproducibility. In contrast, VT caused by the reentrant mechanism can result in successful termination using programmed stimulation, without excluding triggered activity.[18]

The efficacy of ATP in these VTs may be explained by the fact that the VT mechanisms were based on reentry, and that VTs that demonstrate poor response to ATP therapy result from the lack of organized reentry.

4.1 VT termination

In our study, the successful VT termination rate using ATP was 85%, which is equivalent to those reported

in previous studies.[19,20] In cases of faster VT, the rate was lower since a faster VT has a shorter excitable gap in the reentrant circuit; hence, it is more difficult for the pacing stimulus to enter the circuit.[21] VT classification, based on the variability of the VT cycle length, revealed that the successful termination rate following ATP therapy was 94% in regular VTs and 65% in irregular VTs with statistical significance. We observed that VTs with stable cycle length variability are more likely to respond to ATP therapy.

Spontaneous termination after ATP delivery or without therapy was found significantly more often in irregular than in regular VTs. Spontaneous termination after ATP delivery can include purely spontaneous termination and termination due to overdrive pacing, which is a characteristic finding of non-reentrant mechanisms.[22]

Furthermore, no significant differences were found between patients with ischemic and non-ischemic cardiomyopathies with respect to VT termination using ATP therapy. Scar-related reentry is the most common cause of sustained VT in the presence of structural heart disease.[23] In patients with structural heart disease, myocardial infarction is most commonly associated with a damaged myocardium, which serves as a substrate for reentrant arrhythmias. However, scar-related VT also develops in other myocardial diseases, including dilated cardiomyopathy, sarcoidosis, and arrhythmogenic right ventricular cardiomyopathy, and after cardiac surgery for congenital heart disease or valve replacement.[17] The scar slows conduction and increases susceptibility to reentrant arrhythmias.

4.2 Clinical implication of RR interval variability of VT on ICD management.

Since VT regularity is highly reproducible in an episode or in an individual, it could be possible to construct more effective ICD settings according to the RR interval variability of VT (i.e. considering aggressive ATP therapy for regular VTs and extending the VT detection time and initiation of therapy in cases of irregular VTs).

In addition, it could be possible to develop a more effective algorithm based on the variability of the RR interval. Further research is needed for this purpose.

5 LIMITATIONS

First, the number of VT episodes per individual varies. Multilevel logistic regression was applied to estimate the odds ratio, since VT episodes were nested within individuals. Second, the VT evaluation period was limited to 10 RR intervals of 2 seconds after the onset, to simplify clinical usage. In some episodes, RR interval variations may have changed after the assessment. Third, we could not perform multivariate analysis for spontaneous termination without therapy since the number of target episodes was small. Fourth, these results may not hold true for slow VT because the programming of VT detection for each monitor and therapy zone was set at approximately 150 bpm in most episodes.

6 CONCLUSIONS

ATP therapy for VT termination is more effective for regular than for irregular VT, as determined by the simple methodology. Additionally, irregular VT has a higher rate of spontaneous termination than regular VT, and the VT cycle length variability is reproducible for both an episode and an individual.

Acknowledgments: None.

References

1. Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997;337:1576–1583.
2. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med 1996;335:1933–1940.

3. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877–883.
4. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. N Engl J Med 1999;341:1882–1890.
5. Poole JE, Johnson GW, Hellkamp AS, et al. Prognostic importance of defibrillator shocks in patients with heart failure. N Engl J Med 2008;359:1009–1017.
6. Sweeney MO, Sherfesee L, DeGroot PJ, Wathen MS, Wilkoff BL. Differences in effects of electrical therapy type for ventricular arrhythmias on mortality in implantable cardioverter-defibrillator patients. Heart Rhythm 2010;7:353–360.
7. Wathen MS, DeGroot PJ, Sweeney MO, et al. Prospective randomized multicenter trial of empirical antitachycardia pacing versus shocks for spontaneous rapid ventricular tachycardia in patients with implantable cardioverter-defibrillators: Pacing Fast Ventricular Tachycardia Reduces Shock Therapies (PainFREE Rx II) trial results. Circulation 2004;110:2591–2596.
8. Anguera I, Dallaglio P, Martínez-Ferrer J, et al. Shock reduction with multiple bursts of antitachycardia pacing therapies to treat fast ventricular tachyarrhythmia in patients with implantable cardioverter defibrillators: A multicenter study. J Cardiovasc Electrophysiol 2015;26:774–782.
9. Sanders P, Connolly AT, Nabutovsky Y, Fischer A, Saeed M. Increased hospitalizations and overall healthcare utilization in patients receiving implantable cardioverter-defibrillator shocks compared with antitachycardia pacing. J Am Coll Cardiol EP 2018;4:243–253.
10. Gulizia MM, Piraino L, Scherillo M, et al. A randomized study to compare ramp versus burst antitachycardia pacing therapies to treat fast ventricular tachyarrhythmia in patients with implantable cardioverter defibrillators: The PITAGORA ICD trial. Circ Arrhythm Electrophysiol 2009;2:146–153.
11. Fang Y, Gu K, Yang B, et al. What factors lead to the acceleration of ventricular tachycardia during antitachycardia pacing?-Results from over 1000 episodes. J Arrhythm 2017;34:36–45.
12. Garcia-Alberola A, Yli-Mäyry S, Block M, et al. RR interval variability in irregular monomorphic ventricular tachycardia and atrial fibrillation. Circulation 1996;93:295–300.
13. Oginosawa Y, Kohno R, Honda T, et al. Superior rhythm discrimination with the SmartShock technology algorithm - results of the implantable Defibrillator With Enhanced Features and Settings for Reduction of Inaccurate Detection (DEFENSE) Trial. Circ J 2017;81:1272–1277.
14. Duncker D, Veltmann C. Optimizing antitachycardia pacing: back to the roots. Circ Arrhythm Electrophysiol 2017;10: number 9.
15. Riley MP, Marchlinski FE. ECG clues for diagnosing ventricular tachycardia mechanism. J Cardiovasc Electrophysiol 2008;19:224-229.
16. Jiménez-Candil J, Hernández J, Martin A, et al. Influence of cycle length variations on antitachycardia pacing effectiveness among ICD patients. Heart Rhythm 2013;10:207–213.
17. Tuan TC, Lo MT, Lin YJ, et al. The use of signal analyses of ventricular tachycardia electrograms to predict the response of antitachycardia pacing in patients with implantable cardioverter-defibrillators. J Cardiovasc Electrophysiol 2014;25:411–417.
18. Cronin EM, Bogun FM, Maury P, et al. 2019 HRS/EHRA/APHRS/LAHRS expert consensus statement on catheter ablation of ventricular arrhythmias. Heart Rhythm 2020;17:e2–154.
19. Joung B, Lexcen DR, Ching CK, et al. Additional antitachycardia pacing programming strategies further reduce unnecessary implantable cardioverter-defibrillator shocks. Heart Rhythm 2020; 7:98–105.
20. Cantillon DJ, Wilkoff BL. Antitachycardia pacing for reduction of implantable cardioverter-defibrillator shocks. Heart Rhythm 2015;12:1370–1375.
21. Josephson M. Evaluation of electrical therapy for arrhythmias. In: Josephson M, editor. Clinical Cardiac Electrophysiology. Philadelphia, PA: Lippincott Williams & Wilkins, 2008:701.
22. Moak JP, Rosen MR. Induction and termination of triggered activity by pacing in isolated canine Purkinje fibers. Circulation 1984;69:149–162.
23. Kumar S, Romero J, Mehta NK, et al. Long-term outcomes after catheter ablation of ventricular

tachycardia in patients with and without structural heart disease. Heart Rhythm 2016;13:1957–1963.

Figures

Figure 1. (A) Difference in the cycle length variability of VT. The left panel shows a constant cycle length, whereas the right panel shows the variation in the cycle length. (B) Example of multiple VT episodes within an episode.

Regular VTs account for a larger number of VT types, classified by the variability within an episode. The RE value is calculated by dividing the number of regular VTs (6) by the number of total VTs in the episode (6). A-A = atrial cycle length; RE = reproducibility within an episode; Reg = regular; Term. = termination; VF = ventricular fibrillation; VT = ventricular tachycardia; V-V = ventricular cycle length.

Figure 2. A patient with five VT episodes.

Most VTs in all episodes are irregular. The RI value is calculated by dividing the number of irregular VTs in all episodes of patient (11) by the number of total VT episodes of patient (15), i.e., 11/15 = 0.73. I = irregular VT; R = regular VT; RI = reproducibility within an individual; VT = ventricular tachycardia.

Figure 3. Flow chart of patient selection.

ATP = anti-tachycardia pacing; CL = cycle length; VF = ventricular fibrillation; VT = ventricular tachycardia.

Table 1 Characteristics of patients with episodes of ventricular tachycardia

Number of patients	**n = 43**
Male sex	36 (84%)
Ischemic cardiomyopathy	20 (47%)
Non-ischemic cardiomyopathy (DCM/sarcoidosis/HCM/amyloidosis/Brugada S/unclassified)	23 (53%) (10/
NYHA class (I/II/III/IV)	(12/19/11/1)
ß-blocker use	31 (72%)
ACE-I or ARB use	28 (65%)
Cardiotonic agent use	7 (16%)
Antiarrhythmic drug use	13 (30%)
EF (%)	36, SD*: 15
CRT-D	16 (37%)

Data are presented as n, unless otherwise indicated.

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; Brugada S = Brugada syndrome; CRT-D = cardiac resynchronization therapy defibrillator; DCM = dilated cardiomyopathy; EF = ejection fraction; HCM = hypertrophic cardiomyopathy; NYHA = New York Heart Association; SD = standard deviation.

Table 2 The relationship between patient background and RR interval variability of VT

	Regular VT	**Irregular VT**
	(N=268)	**(N=197)**
Average VT rate (bpm)	178, SD: 26	178, SD: 22
Male sex	218 (81 %)	176 (89 %)
Ischemic cardiomyopathy	119 (44 %)	75 (38 %)
Antiarrhythmic drug use	74 (28 %)	49 (25 %)
ß-blocker use	198 (74 %)	149 (76 %)

	Regular VT	Irregular VT
ACE-I or ARB use	169 (63 %)	149 (76 %)

Data are presented as n (%), unless otherwise indicated.

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; SD = standard deviation; VT = ventricular tachycardia; bpm = beats per min.

Table 3 Odds ratios of clinical characteristics for termination using ATP therapy

		Univariate analysis	Univariate analysis		
	Odds ratio	**95% confidence interval**	**95% confidence interval**	**p-value**	**p-valu**
Regular VT	5.94	2.50	14.13	14.13	< 0.00
Average VT rate (bpm)	0.97	0.95	0.99	0.99	0.006
Male sex	0.59	0.08	4.40	4.40	0.609
Ischemic cardiomyopathy	0.63	0.12	3.45	3.45	0.597
Antiarrhythmic drug use	0.86	0.15	4.99	4.99	0.864
β-βλοςκερ υσε	0.51	0.07	3.48	3.48	0.491
ACE-I or ARB use	1.10	0.20	6.12	6.12	0.914

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ATP = anti-tachycardia pacing bpm = beats per min; VT = ventricular tachycardia.

Table 4 Odds ratios of clinical characteristics for spontaneous termination after ATP delivery

		Univariate analysis	Univariate analysis		
	Odds ratio	**95% confidence interval**	**95% confidence interval**	**p-value**	**Odds**
Irregular VT	29.86	5.95	149.80	< 0.001	30.58
Average VT rate (bpm)	0.99	0.97	1.02	0.662	1.00
Male sex	1.42	0.15	13.60	0.609	1.81
Ischemic cardiomyopathy	1.70	0.25	11.67	0.590	0.83
Antiarrhythmic drug use	1.05	0.15	7.48	0.958	0.91
β βλοςκερ υσε	1.55	0.17	13.75	0.694	1.86
ACE-I or ARB use	1.01	0.14	7.05	0.993	0.96

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ATP = anti-tachycardia pacing; bpm = beats per min; VT = ventricular tachycardia. **Table 5 Odds ratios of clinical characteristics for acceleration of VTs**

		Univariate analysis	Univariate analysis		
	Odds ratio	**95% confidence interval**	**95% confidence interval**	**p-value**	**Odds**
Regular VT	1.09	0.32	3.79	0.887	1.13
Average VT rate (bpm)	1.04	1.01	1.06	0.008	1.04
Male sex	1.22	0.10	15.16	0.879	2.64
Ischemic cardiomyopathy	1.39	0.16	12.07	0.765	1.48
Antiarrhythmic drug use	1.45	0.16	12.94	0.738	1.96
β-βλοςκερ υσε	3.03	0.24	38.59	0.393	7.17
ACE-I or ARB use	0.55	0.06	4.74	0.590	0.27

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; bpm = beats per min; VT = ventricular tachycardia.

Supplementary Table 1 Recommended programing

	Status	**Criteria**	**Therapy**
Zone			
Ventricular fibrillation	On	Cycle length; no. of intervals to detection	Physician discretion
Ventricular tachycardia	On	Cycle length < 400 ms; No. of intervals to detection: 16 Re-detection: 12	Physician discretion
SVT limit zone		Physician discretion	
PR-Logic	On		
Wavelet	On or monitor		
Discriminator			
T-wave oversensing	On		
Lead noise	On or on + timeout		

Supplementary Table 2 Characteristics of ATP therapy

		All VT episodes	**All VT episod**
Episodes of ATP therapy	290	290	196 (68%)
Initial R-S1 interval (%RR) (91/88/84/81)	(12/221/14/43)	(12/221/14/43)	(6/145/8/37)
Initial pulses (4/6/8/12/14)	(1/3/231/52/3)	(1/3/231/52/3)	(1/3/147/45/0)
Included ramp pacing	5	5	3 (2%)
Average VT rate targeted by ATP therapy (bpm)	179	179	179
ATP times for termination of VT without shock therapy	1.35 times	1.35 times	1.35 times
Termination by ATP therapy	246 (85%)	246 (85%)	184 (94%)
Acceleration after ATP therapy	16	16	9 (5%)
Uncaptured VT episodes by ATP (burst/ramp)	(5/1)	(5/1)	(4/0)

Data are presented as n, unless otherwise indicated.

ATP, anti-tachycardia pacing; bpm, beats per min; VT, ventricular tachycardia.

Hosted file

`Fig_1.pdf` available at https://authorea.com/users/336039/articles/500835-rr-interval-variability-in-the-evaluation-of-ventricular-tachycardia-and-effects-of-implantable-cardioverter-defibrillator-therapy

Hosted file

`Fig_2.pdf` available at https://authorea.com/users/336039/articles/500835-rr-interval-variability-in-the-evaluation-of-ventricular-tachycardia-and-effects-of-implantable-cardioverter-defibrillator-therapy

Hosted file

`Fig_3.pdf` available at https://authorea.com/users/336039/articles/500835-rr-interval-variability-in-the-evaluation-of-ventricular-tachycardia-and-effects-of-implantable-cardioverter-defibrillator-therapy