Fast rate (≥ 250 beats/min) right ventricular burst stimulation is useful for ventricular tachycardia induction in arrhythmogenic right ventricular cardiomyopathy

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Abstract

Background One of the major challenges in arrhythmogenic right ventricular cardiomyopathy (ARVC) ablation is ventricular tachycardia (VT) non-inducibility. The study aimed to assess whether fast rate (≥ 250 beats/min) right ventricular burst stimulation was useful for VT induction in patients with ARVC. Methods Ninety-one consecutive ARVC patients with clinical sustained VT that underwent electrophysiological study were enrolled. The stimulation protocol was implemented at both right ventricular apex and outflow tract as follows: Step A, up to double extra-stimuli; Step B, incremental stimulation with low rate (< 250 beats/min); Step C, burst stimulation with fast rate (≥ 250 beats/min); Step D, repeated all steps above with intravenous infusion of isoproterenol. Results A total of 76 patients had inducible VT (83.5%), among which 49 were induced by Step C, 15 were induced by Step B, 8 and 4 by Step A and D, respectively. Clinical VTs were induced in 60 patients (65.9%). Only two spontaneously ceased ventricular fibrillations were induced by Step C. Multivariate analysis showed that a narrower baseline QRS duration under sinus rhythm was independently associated with VT non-inducibility (OR: 1.1; 95% CI: 1.0–1.1; P = 0.019). Conclusion Fast rate (≥ 250 beats/min) right ventricular burst stimulation provides a useful supplemental method for VT induction in ARVC patients.

Keywords: Burst stimulation; Cardiomyopathy; Right ventricular; Ventricular tachycardia

1 Introduction

During the past decade, radiofrequency catheter ablation has emerged as an effective therapy for ventricular tachycardia (VT) in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC).1–3 One of the major challenges in mapping and ablation is VT non-inducibility.4 Although conventional VT induction protocols including extra-stimuli and low rate (< 250 beats/min), incremental stimulation were widely used, a considerable number of patients were still non-inducible.5,6

The anatomic and electrophysiological substrates of VT vary widely in different diseases, which may lead to inconsistent results of VT induction. Fast rate (≥ 250 beats/min) burst stimulation is rarely used for VT induction in structural heart diseases for security consideration. In particular, few study focused on this field in ARVC due to the low prevalence up to now. This study aimed to evaluate the value of fast rate (≥ 250 beats/min) right ventricular burst stimulation for VT induction in ARVC, which was by no mean to deny the conventional VT induction protocols but just wanted to contribute an additional tool.

2 Methods

2.1 Study population

From November 2005 to July 2013, 91 consecutive ARVC patients with clinical sustained monomorphic VT who underwent electrophysiological study were enrolled. The exclusion criteria included: (1) patients who had previous VT ablation history; and (2) patients whose VTs were spontaneous or induced by mechanical stimulation during the catheterization. Sustained VT was defined as continuous...
VT for at least 30 s or that required an intervention for termination such as cardioversion.\[4\]

At the beginning of the study, the diagnosis of ARVC was based on the criteria set by the Task Force of the Working Group of Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology.\[7\] The 2010 revised Task Force Criteria was employed to enroll new patients after published, and the previous enrolled patients were re-checked according to the 2010 revised Task Force Criteria,\[8\] patients who were not meet the revised criteria were excluded. The study was approved by the local ethical research committee. Informed consent was obtained from all patients.

2.2 Electrophysiological study

All antiarrhythmic drugs were discontinued at least five half-lives prior to electrophysiological study except amiodarone. All patients received local anesthesia with lidocaine. Surface electrocardiogram and bipolar endocardial electrogram were continuously monitored and recorded (Bard Electrophysiology, Lowell, MA, USA). The pacing stimuli were 2 ms in duration and twice diastolic threshold current in strength. The stimulation protocol was implemented stepwise at both right ventricular apex and outflow tract as follows: first, up to double extra-stimuli (step A). Patients who failed to induce received low rate (< 250 beats/min) incremental stimulation (step B). In patients whose VT was not induced, fast rate (≥ 250 beats/min) burst stimulation was performed (step C). Finally, step D was given in patients whose VT were still failed to induce, which repeated all steps above sequential during an intravenous infusion of isoproterenol. The isoproterenol was infused at a rate of 1–6 μg/min in order to increase the heart rate by at least 30%. All steps above were performed only once.

For step A, single extra-stimuli (S2) were introduced with an initial coupling interval of 400 ms after eight driven beats at a cycle length of 500 ms. Double extra-stimuli (S2, S3) were performed with S2 initially positioned 30 ms beyond ventricular refractoriness, and initially positioned 300 ms beyond S2. The coupling intervals of extra-stimuli were shortened by 10 ms decrements. For step B, incremental stimulation was performed at rate of 150–240 beats/min for 10 s, and for step C, stimulation were performed for 10 beats and increased by 10 beats/min increments. The endpoints were: (1) sustained VT was induced; and (2) the ventricular refractoriness was reached.

The morphology and rate of the induced VT was compared with the electrocardiogram of the clinical VT. The QRS duration including fragmented QRS was measured using an electric caliper. The definition of a fragmented QRS complex was deflections at the beginning of the QRS complex, on top of the R-wave, or in the nadir of the S-wave similar to the definition previously used in coronary diseases.\[9\] All electrocardiogram analyses were performed by the agreement of two independent readers blinded to patient characteristics and induction results.

2.3 Statistical analysis

Statistical analyses were performed using SPSS 19.0 software (SPSS Inc, Chicago, Illinois, USA). Comparisons of continuous variables between groups were performed with the Student’s t-test or Wilcoxon test. Chi-square analysis was used to compare the categorical variables between groups. For the multivariate logistic regression analysis, the following variables including sex, age, amiodarone use, baseline QRS duration under sinus rhythm, VT history, number and rate of clinical VT, left ventricular ejection fraction (LVEF) and right ventricle (RV) dilatation were analyzed to evaluate in association with VT inducibility. All tests were two-tailed and statistical significance was established at a P < 0.05.

3 Results

3.1 Patient characteristics

From November 2005 to July 2013, 127 ARVC patients with clinical sustained monomorphic VT underwent electrophysiological study in our institution. Among which, 22 patients had previous VT ablation history and 14 patients whose VTs were spontaneous or induced by mechanical stimulation during the catheterization. The remaining 91 patients were enrolled (72 male; age 40.5 ± 12.3 years). The mean age at first presentation of symptoms was 36.0 ± 12.3 years (range: 8–66 years), and 27 (29.7%) patients had more than one type of VT. The baseline characteristics of the enrolled 91 patients were presented in Table 1.

3.2 Mode and predictive factors of VT induction

The outcomes of VT induction were summarized in Table 2. A total of 76 (83.5%) patients had inducible VTs, among which 49 were induced by step C, 15 were induced by step B whereas 8 and 4 by step A and D, respectively. In details, only 8 (8.8%) patients had inducible VTs by step A. However, in those patients who were failed to induce by step A and B, 49 (72.1%) had inducible VTs by step C. Eighteen patients who failed to induce by step A, B, and C were performed with step D, while VT was induced in four patients (Figure 1).
Table 1. The baseline characteristics of the cohort.

|                        | Total (n = 91) | Inducible (n = 76) | Non-inducible (n = 15) | P-value |
|------------------------|----------------|--------------------|------------------------|---------|
| Age, yr                | 40.5 ± 12.2    | 40.5 ± 12.5        | 40.1 ± 11.1            | 0.666   |
| Sex, M/F               | 72/19          | 62/14              | 10/5                   | 0.194   |
| Amiodarone use         | 9 (9.9%)       | 7 (9.2%)           | 2 (13.3%)              | 0.639   |
| Median QRS duration, ms| (72–168)       | (72–168)           | (78–128)               | 0.002   |
| Clinical VT            |                |                    |                        |         |
|                       |                |                    |                        |         |
| Datum                  | 24 (1–228)     | 24 (1–228)         | 48 (12–120)            | 0.732   |
| ≥ 1 type of VT         | 27 (29.7%)     | 23 (30.3%)         | 4 (26.7%)              | 0.781   |
| Median rate, beats/min | (120–310)      | (120–310)          | (170–280)              | 0.166   |
| Median number, n       | 1 (1–4)        | 1 (1–4)            | 1 (1–3)                | 0.798   |
| RV dilatation          | 66 (72.5%)     | 56 (73.7%)         | 10 (66.7%)             | 0.578   |
| Hypertension           | 13 (14.3%)     | 10 (13.2%)         | 2 (13.3%)              | 0.985   |
| Diabetes mellitus      | 5 (5.5%)       | 4 (5.3%)           | 1 (6.7%)               | 0.827   |

Data are presented as n (%), mean ± SD, or median (range) unless other indicated. *RV dilatation was defined as RV transverse diameter ≥ 40 mm in four-chamber view in the end-diastolic. LVEF: left ventricular ejection fraction; RV: right ventricle; VT: ventricular tachycardia.

Table 2. The results of VT induction by each stimulation step.

| Step A (n = 91) | Step B (n = 83) | Step C (n = 68) | Step D (n = 19) |
|----------------|----------------|----------------|----------------|
| Patients with VT | 8 (8.8%)       | 15 (18.1%)     | 49 (72.1%)     | 4 (21.1%) |
| Clinical VT     | 7 (7.7%)       | 12 (14.5%)     | 38 (55.9%)     | 3 (15.8%) |
| Nonclinical VT  | 1 (1.1%)       | 3 (3.6%)       | 11 (16.2%)     | 5 (5.3%)  |
| Specificity, %  | 87.5%          | 80.0%          | 77.6%          | 75%       |
| Median rate of VT, beats/min | 175          | 170           | 220            | 225       |
| VF              | 130–220        | 150–210        | 140–280        | 190–230   |
| Non-inducible   | 83 (91.2%)     | 68 (81.9%)     | 18 (21.7%)     | 15 (78.9%) |

Data are presented as n (%), or median (range) unless other indicated. *The specificity represented the proportion of induced clinical VT counts in total induced VT. VF: ventricular fibrillation; VT: ventricular tachycardia.

Clinical VTs were induced in 60 (65.9%) patients, which accounted for 78.9% of the total number of the study cohort. The proportions of clinical VTs were 7/8, 12/15, 38/49 and 3/4 in step A, B, C and D, respectively, significant statistical difference was not found among each step (P = 0.928). Of note was that VTs induced by step C were faster than those by step A and B (P = 0.001).

For step B and step C, the median induction conditions were 215 and 280 beats/min, respectively. It was worth men-
protocols in detail and showed that fast rate right ventricular burst stimulation was feasible in a large number of ARVC patients. Application of the fast rate right ventricular burst stimulation protocol would be a useful supplement for VT induction in order to facilitate ablation.

Although conventional VT induction protocols including extra-stimuli and incremental stimulation (< 250 beats/min) had been found to increase the yield of inducible VT in a group of diseases, a number of variables including different numbers of extra-stimuli, drive cycle length, current strength and sites of stimulation have been performed, lack of control of those variables has led to a significant variability in reported sensitivity, specificity and reproducibility.[6,10] Furthermore, there were still a considerable number of patients who were non-inducible despite combined a number of protocols in patients with ARVC. This study showed that fast rate right ventricular burst stimulation was an effective and safe supplementary protocol for VT induction in ARVC.

The multi-formity in anatomic and electro-physiologic substrates contributed to different mechanisms of VT. In ischemic cardiomyopathy, the border zone of infarcted myocardium were shown to be an area of relatively slow conduction with highly heterogeneous recovery of excitability and activation times, which provided the substrate for the formation of functional block lines that could promote reentry.[11-13] VT in ischemic cardiomyopathy could be reproducibly induced by extra-stimuli, which were considered as a hallmark of reentrant arrhythmia.[14] However, the anatomic and electrophysiologic substrates of VT in ARVC were less clear. Although previous studies showed VT in ARVC was characterized by areas of slow conduction within the diseased myocardium which allow continuous electrical activity in an expanded area, creating a circuit pathway.[15] Our study showed that the majority of clinical VTs could be induced easily by fast rate burst stimulation, which might support that localized mechanism including micro-reentry and triggered activity might be the main mechanism of VT in ARVC. Previous studies found that fragmented diastolic potentials were recorded in 94% of ARVC patients, and the rate of inducible VTs was up to 93% by extra-stimuli, comparing to 3% in patients with idiopathic VT whose main mechanism was triggered activity.[16,17] O’Donnell, et al.[18] found that 82% of the VT was induced by up to five extra-stimuli, and the mean cycle length of induced VT was 310 ms in ARVC patients, which was slower than by fast burst stimulation in our study. The differences indicated that the mechanisms of VT in ARVC patients were diverse, extra-stimuli might be effective to induce relatively slower macro-reentry VT in ARVC, while fast rate burst stimulation might be useful for fast VT due to mechanism of micro-reentry or triggered activity.

The value of isoproterenol for VT induction largely depended on the mechanism of VT. The pharmacological mechanisms indicate that isoproterenol was useful for the induction of exercise-induced VT which mainly based on triggered activity. Freedman, et al.[19] found that facilitation of VT induction by isoproterenol might be up to 20% in a group of diseases. Josephson suggested that isoproterenol has a low yield (less than 5%) in coronary disease patients with sustained VT,[20] because the main mechanism of ischemic cardiomyopathy VT is macro-reentry, which does not depend on catecholamine concentrations.[21,22] Philips, et al.[23] reported a high degree of association between premature ventricular contractions at baseline and the VTs induced during the use of high dose isoproterenol in patients with ARVC, which indicated that high dose isoproterenol infusion could contributes to induce VT in ARVC. A recent study found that ventricular arrhythmogenicity during isoproterenol testing had a high sensitivity of 91.4% for the diagnosis of ARVC, particularly in its early stages.[24] Although the design of this study might underestimate the true yield of induced VT with isoproterenol, the results supported that isoproterenol was useful for VT induction in ARVC. One possible explanation was that isoproterenol could enhance the automaticity of VT triggers.

In addition to the specific methodological features of stimulation protocols, some clinical characteristics might associate with VT induction. This study showed that a narrower QRS duration under sinus rhythm was a risk factor of VT non-inducibility. The reasonable explanation was that wider QRS duration might represent more severe myocardial fibrosis, which could predict fatal and nonfatal arrhythmic events.[25] However, it was worth mentioning that there was a considerable overlap in the duration of QRS complex in patients who were inducible and non-inducible, the predictive value of the QRS duration should be carefully interpreted.

4.1 Limitations

For ethical considerations, we did not randomize patients to different stimulation protocol steps. The design of this study precluded any conclusions regarding the true yield of induced VT with each pacing modality. Furthermore, this study only evaluated up to two extra-stimuli, whereas many electrophysiologists would use three extra-stimuli. However, although three extra stimuli were used, there were still a considerable number of patients who are non-inducible. This study was mainly to provide a supplemental method to those difficult cases, and was the first one that confirmed fast rate ventricular burst stimulation is feasible in ARVC.
4.2 Conclusions

Fast rate (≥ 250 beats/min) right ventricular burst stimulation was often considered unreliable and unsafe but few study validated it in patients with ARVC. Our results showed its safety and it should be a supplementary method for VT induction in ARVC patients, especially in patients who were non-inducible by conventional VT induction protocols. This method will not only facilitate catheter ablation of VT in ARVC, but also add more knowledge to ARVC VT mechanism research.

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