Frequency Characteristics and Associations with the Defibrillation Threshold of Ventricular Fibrillation in Patients with Implantable Cardioverter Defibrillators

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Abstract

Objective The dominant frequency (DF) in frequency analyses is considered to represent the objective cycle length and complexity of activation under conditions of ventricular fibrillation (VF). However, knowledge regarding the mechanisms determining the DF in human VF is limited. We studied the characteristics of the DF of human VF and relationship between DF and the defibrillation threshold.

Methods Seventy-two implantable cardioverter-defibrillator patients and 211 VF were studied. Using defibrillation tests, we performed a frequency analysis with fast Fourier transformation. The correlations between DF and clinical characteristics, including the defibrillation threshold, were assessed.

Results The mean DF of all induced VFs was 5.2±0.8 Hz. The patients were divided into two groups according to DF: the low-DF (DF <5.2 Hz, n=32) and high-DF (DF ≥5.2 Hz, n=40) groups. The frequency of structural heart disease was significantly higher in the low-DF group. In addition, the QRS duration, QT interval and effective refractory period of the right ventricle (RV-ERP) were significantly longer in the low-DF group. A multivariate analysis showed RV-ERP to be the only independent predictor of DF. Excluding patients receiving group III anti-arrhythmic drugs, which are known to have potent defibrillation threshold effects, the defibrillation threshold was significantly lower in the low-DF group (p=0.026).

Conclusion We found that the DF of human VF is associated with underlying heart disease, the cardiac function, cardiac conduction, ventricular refractoriness and defibrillation threshold. Our findings may be useful for identifying and managing patients with a high defibrillation threshold.

Key words: ventricular fibrillation, frequency analysis, dominant frequency, defibrillation threshold

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Introduction

Implantable cardioverter-defibrillators (ICDs) are the most effective therapy for preventing sudden cardiac death from ventricular tachyarrhythmia (1-4). State-of-the-art ICDs that deliver sufficiently high energy can usually terminate ventricular fibrillation (VF). However, in some patients, the ICD fails to achieve defibrillation due to a high defibrillation threshold (5, 6), potentially resulting in critical events (2, 3, 7). Various factors, including antiarrhythmic drugs, the cardiac function and electrolyte abnormalities have been reported to be associated with the defibrillation threshold (8). Furthermore, we previously demonstrated that the short cycle length of VF is associated with a high defibrillation threshold (5).

Frequency analyses are used to investigate the characteristics of VF (9, 10). The dominant frequency (DF) obtained...
from a frequency analysis provides an objective cycle length of VF and is related to the complexity of activation patterns during VF (11, 12). However, frequency analyses of VF have been performed primarily in animal experiments (9, 10), and the characteristics of the DF in human VF remain insufficiently studied. We hypothesized that the DF of VF is associated with clinical factors such as underlying heart disease, the cardiac function and cardiac conductance and may be a determinant of the defibrillation threshold. Therefore, we performed frequency analyses of induced VF in patients with ICD and compared the DF of VF based on clinical factors affecting the defibrillation threshold.

Materials and Methods

Study subjects

We prospectively enrolled patients who underwent ICD/ cardiac resynchronized therapy defibrillator (CRT-D) implantation or generator exchange at our institution between May 2009 and December 2012. The study protocol was approved by the hospital institutional review committee, and all patients provided their written informed consent for ICD implantation and defibrillation testing. All implantation and replacement procedures were performed under local anesthesia with shallow general anesthesia using intravenous propofol anesthesia to avoid the effects of emotional stress on the refractory period. The refractory period was measured using standard techniques of programmed electrical stimulation from the ICD, with trains of eight regular basic stimuli (S1) at pacing cycle lengths of 400 and 600 ms. An extra stimulus (S2) was delivered at a coupling interval (S1S2) shortened in steps of 10 ms. The refractory period was defined as the longest S1S2 interval at which S2 failed to capture the ventricle.

Following measurement of the refractory period, VF was induced by a T-wave shock, and the defibrillation threshold was measured using an up-down algorithm, as shown in Fig. 1 (13, 14). In short, in the first VF induction, the energy of the first defibrillation shock was set at 15J and the second was set at 25J to ensure a safety margin of 10J. Remaining shocks were set at the maximum output of each device. If the 25J shock failed to terminate VF, the defibrillation threshold was considered to be higher than 25J without an adequate safety margin. If the first shock successfully terminated VF, the energy of the first defibrillation shock was decreased to 10J on the second defibrillation test. If the secondary induced VF was terminated by a 10J shock, the defibrillation threshold was determined to be 10J or less. If the 10J shock failed to terminate VF, the defibrillation threshold was classified as 15J. If the first 15J shock failed, the energy of the first defibrillation shock was increased to 20J at the second VF induction. If the secondary induced VF was terminated by a 20J shock, the defibrillation threshold was determined to be 20J. If the 20J shock failed to terminate VF and the following 25J shock terminated VF successfully, the defibrillation threshold was classified as 25J. An external defibrillator was prepared in case defibrillation with ICD failed. An interval of at least five minutes was provided between the first and second defibrillation tests. In addition to defibrillation testing during the operation, we repeated the same test before discharge (approximately two weeks after the operation). Patients who exhibited atrial fibrillation at the time of defibrillation testing were excluded from the study to avoid contaminating the VF waveform with the signal of atrial fibrillation.

Frequency analysis of induced VF

Lead II body surface ECG recordings were digitized at a sampling rate of 1,000 Hz using a WE7000 analog-to-digital converter (Yokogawa Electric, Tokyo, Japan) and stored on a personal computer for the off-line analysis. We used the traces of lead II for the following reasons: 1) our system for the frequency analysis could deal with only one lead of the surface ECG; 2) there may be spatial differences in the DF in the whole heart (15), such that we thought it would be better to use one of the limb leads to reduce the influence of the spatial difference on the DF. Fast Fourier transformation was used to calculate the DF of induced VF over five seconds before defibrillation, the employing Xviewer 701992 software program (Yokogawa Electric). This system provides the power spectrum of frequencies included in the induced VF with a resolution of 0.2 Hz. The DF was defined as the
Figure 1. Algorithm for measurement of the defibrillation threshold. In the first VF induction, the energy of the first defibrillation shock was set at 15J and the second was set at 25J. Remaining shocks were set at the maximum output of each device. In the following VF induction, the energy of each shock was set according to the results of the first VF induction.

| Characteristic                  | Value |
|--------------------------------|-------|
| Age (years)                    | 60 ± 15                        |
| Male gender, n (%)             | 56 (77)                        |
| Underlying heart disease, n (%)|       |
| Dilated cardiomyopathy         | 13 (18)                        |
| Coronary artery disease        | 9 (13)                         |
| Hypertrophic cardiomyopathy    | 5 (7)                          |
| Cardiac sarcoidosis            | 6 (10)                         |
| ARVC                           | 2 (3)                          |
| Idiopathic VF/VT               | 12 (17)                        |
| Brugada syndrome               | 14 (19)                        |
| Others                         | 11 (15)                        |
| LV ejection fraction (%)       | 52 ± 19                        |
| Medication, n (%)              |       |
| Beta-adrenergic blocker, n (%) | 48 (67)                        |
| class I AAD, n (%)             | 4 (6)                          |
| Amiodarone, n (%)              | 6 (8)                          |
| Sotalol, n (%)                 | 6 (8)                          |

ARVC: arrhythmogenic right ventricular cardiomyopathy, AAD: anti-arrhythmic drug

Results

Clinical characteristics of the patients

The clinical characteristics of the 72 study subjects in this study are presented in Table 1. The mean age was 60±15 years, and 77% of the subjects were men. A total of 46 of the 72 patients (64%) had structural heart disease, including non-ischemic dilated cardiomyopathy (n=13), ischemic heart disease (n=9), cardiac sarcoidosis (n=6), hypertrophic cardiomyopathy (n=5), arrhythmogenic right ventricular cardiomyopathy (n=2) and other heart diseases (n=11), while the remaining 26 had arrhythmia syndromes without structural heart abnormalities. The mean left ventricular ejection fraction (LVEF) was 52±19%. Beta-adrenergic blockers were prescribed in 48 patients (67%). Class I and III anti-arrhythmic drugs were used in four (6%) and 12 patients (16%), respectively. ICDs/CRT-Ds were implanted for secondary prevention in 58 patients (81%). All of the 211 induced VFs were successfully defibrillated with ≤25J shocks, and thus no patients had a defibrillation threshold of >25J (mean defibrillation threshold, 12.4±4.6J).
Case A: Idiopathic VF

![Figure 2](image1.png)

**Figure 2.** Frequency analysis of induced ventricular fibrillation (VF). A: Frequency analysis in a patient with idiopathic VF. The dominant frequency was relatively high, reaching 5.8 Hz just before defibrillation. B: Frequency analysis in a patient with dilated cardiomyopathy. The dominant frequency was relatively low throughout the ongoing episode of VF.

Case B: Dilated cardiomyopathy

![Figure 3](image2.png)

**Figure 3.** Distribution of the dominant frequency in induced ventricular fibrillation (VF). The mean dominant frequency was 5.2±0.8 Hz (range, 3.4 to 7.4 Hz).

**DF of induced VF**

Typical results of the frequency analysis are presented in Fig. 2. The mean DF of all VF was 5.2±0.8 Hz (range, 3.4 to 7.4 Hz), and the distribution of the DF is presented in Fig. 3. The DF was greater in the patients without structural heart disease (5.8±0.5 Hz, n=26) than in the patients with structural heart disease (4.8±0.6 Hz, n=46) (p<0.001).

**Clinical factors associated with the DF**

The patients were divided into two groups according to the DF of the induced VF (the group with a lower DF than the mean DF of all VF (low-DF group, DF <5.2 Hz, n=32) and the group with a higher DF than the mean DF of all VF (high-DF group, DF ≥5.2 Hz, n=40)) and the clinical characteristics were compared between the two groups (Table 2). The prevalence of structural heart disease was higher in the low-DF group (94%) than in the high-DF group (40%, p<0.001). The left ventricular ejection fraction was lower in the low-DF group than in the high-DF group. Compared to that observed in the high-DF group, the QRS duration, QT and corrected QT intervals and right ventricular refractory period were longer in the low-DF group. Treatment with beta-adrenergic blockers and sotalol was more common in the low-DF than the high-DF group.

As shown in Fig. 4, the QRS duration, QT interval, right ventricular refractory period and left ventricular ejection fraction were significantly correlated with the DF, consistent with prior results of this study. The presence of structural heart disease and use of class III anti-arrhythmic drugs (amiodarone and sotalol) and beta-adrenergic blockers were also associated with the DF (Table 3). In the multivariate analysis, only the right ventricular refractory period was associated with the DF (p=0.0004).

**Correlation between the DF and defibrillation threshold**

In this study, all patients achieved a safety margin of >10 J. The mean defibrillation threshold of all patients was 12.4±4.6J. There were no differences in the defibrillation threshold between the two groups with high and low dominant frequencies (Table 4). After excluding patients treated with class III anti-arrhythmic drugs (amiodarone and sotalol, n=12), which have potent effects on the defibrillation thresh-
The main findings of this study are as follows: 1) the presence of structural heart disease and the cardiac function, QRS duration, QT interval and right ventricular refractory period were associated with the DF of induced VF and 2) a high DF was associated with a high defibrillation threshold.

**Distribution of the DF in human VF**

The mean DF was 5.2±0.8 Hz, with a distribution range from 3.4 to 7.4 Hz, consistent with the results of previous studies (5.8±1.8 Hz in patients undergoing bypass surgery, and 4.87 to 5.34 Hz in patients undergoing ICD implantation) (12, 16). The DF is an objective measurement of the cycle length of VF (16). The DF ranging from 3.4 to 7.4 Hz observed in this study is equivalent to a heart rate from 204 to 444 beats per minutes, and thus the nominal threshold of VF detection around 190 beats per minutes is reasonable. Indeed, all induced VFs in this study were higher than 200 beats per minute.

**Determinants of the DF**

The DF has been reported to be associated with the length of the reentrant circuit, conduction velocity and refractory period in the ventricles (16). Indeed, in this study, the DF was associated with the QRS duration, QT interval and effective refractory period. Furthermore, patients who received class III drugs that prolong the refractory period had a low DF, similar to the findings of a previous experimental study (17). It is interesting to note that the effective refractory period exhibited a stronger correlation with the DF than the QT interval despite the fact that both the effective refractory period and QT interval reflect the action potential duration in cardiomyocytes. The duration of the action potential correlates with the duration of the preceding diastolic interval (action potential duration restitution), and the restitution kinetics has been shown to participate in the initiation and maintenance of ventricular fibrillation (18). Hence, the effective refractory period measured with the shortest coupling interval, instead of the QT interval on resting ECG, may better represent the behavior of cardiomyocytes during ventricular fibrillation with an extremely short cycle length. Cardiac dysfunction and structural heart abnormalities may affect the DF via alterations in the ventricular size, cardiac conduction and refractory period. In this study, the presence of structural heart disease and cardiac dysfunction was associated with the DF. However, the dimension or wall thickness of the left ventricle did not affect the DF. The wavelength, a product of the refractory period and conduction velocity, is a critical determinant of reentry (17). In the multivariate analyses, the effective refractory period of the right ventricle, which expresses the refractoriness of the myocardium, was found to be associated with the DF, whereas the QRS interval, which reflects cardiac conduction, was not. The refractory period may play an important role as a substrate for VF compared to the conduction velocity;
Figure 4. Correlations between the dominant frequency and clinical characteristics. The QRS duration, QT interval and right ventricular refractory period were negatively correlated with the dominant frequency [(a), (c), and (d)], while the left ventricular ejection fraction was positively correlated with the dominant frequency (b). RV-ERP: right ventricular refractory period

Table 3. Correlation between Dominant Frequency and Clinical Characteristics.

| Variable                        | p value |         |         |
|---------------------------------|---------|---------|---------|
| Presence of SHD                 | <0.0001 | NS      |
| LV ejection fraction            | 0.0002  | NS      |
| QRS duration                    | 0.009   | NS      |
| QT interval                     | 0.017   | NS      |
| RV-ERP                          | <0.0001 | 0.0004  |
| Medication with Beta-adrenergic blocker | 0.003 | NS      |
| Medication with group III AAD   | <0.0001 | NS      |

NS: not significant, SHD: structural heart disease, RV: right ventricle, ERP: effective refractory period, LV: left ventricle, AAD: anti-arrhythmic drug

however, whether the QRS interval during sinus rhythm reflects the conduction velocity during VF is unclear.

Association between the DF and defibrillation threshold

Structural heart abnormalities, such as cardiac dysfunction and left ventricular hypertrophy, have been suggested to be associated with the defibrillation threshold (19, 20). Among electrophysiological properties, the cycle length of VF correlates with the defibrillation threshold in the canine heart (21), and we have previously reported that a short ventricular refractory period and short cycle length of VF are associated with a high defibrillation threshold in patients with Brugada syndrome (5). Furthermore, in the current study, a high DF was found to be associated with an increased defibrillation threshold. Previous studies have shown that the DF is related to the degree of organization of wave patterns during VF (11, 12) and that the extent of organization determines the energy requirements for successful defibrillation (22). The mechanisms by which the degree of organization of arrhythmia affects the probability of success for a given shock strength remain unclear. However, experimental and computational studies have demonstrated that a larger number of functional reentries results in an increased defibrillation threshold based on two factors: 1) the magnitude of virtual electrode polarization in the tissue depth and 2) the difference in the preshock electrophysiological state of the tissue (23, 24). Specifically, a smaller magnitude of virtual electrode polarization in the tissue depth leads to the formation of intramural postshock excitable pathways, and significant dispersion of postshock refractoriness due to the difference in the preshock electrophysiological state results
in wave breaks of the intramural postshock wave front followed by the recurrence of VF. It is assumed that there is a larger number of functional reentries during VF with a high DF. Therefore, refibrillation may easily occur.

**Clinical implications**

In this study, all patients achieved an adequate safety margin for the defibrillation threshold. However, previous studies have reported clinical problems associated with an extremely high defibrillation threshold in 1-8% of ICD patients (25). An extremely high defibrillation threshold may result in the failure of therapy for life-threatening arrhythmia. A previous study showed that a high defibrillation threshold correlates with age, heart rate, left ventricular mass, left ventricular ejection fraction, New York Heart Association class and amiodarone use (25). In the present study, we demonstrated a correlation between the DF and defibrillation threshold in the setting of human VF. In addition, we found the ventricular refractory period to be the most powerful determinant of the DF. Whether the ventricular refractory period directly correlates with the defibrillation threshold remains unclear, and the present study was not designed to address this issue. Nevertheless, our results provide meaningful insight into the intriguing relationship between the ventricular refractory period and defibrillation threshold. Previous studies have shown that some class III anti-arrhythmic drugs decrease the defibrillation threshold by prolonging the ventricular refractory period (8, 26-28). Our results may support the use of class III antiarrhythmic drugs as a therapeutic option for decreasing the defibrillation threshold in patients with an extremely high defibrillation threshold. However, clinicians must be careful about differences in the effect of different class III antiarrhythmic drugs on the defibrillation threshold. Most class III antiarrhythmic drugs, including sotalol, nifekalant and ibutilide, have been reported to decrease the defibrillation threshold (8, 26-29), whereas amiodarone may increase the defibrillation threshold adversely (8). In the present study, the mean defibrillation threshold in the patients on amiodarone (16.7±6.0J, n=6) was higher than that observed in the patients treated without any class III antiarrhythmic drugs (11.9±4.2J, n=59) (p=0.01). In addition, the mean defibrillation threshold in the patients on sotalol (12.1±5.7J, n=7) was as low as that noted in the patients treated without class III antiarrhythmic drugs (11.9±4.2J, n=59) (p=0.91). Therefore, we believe that class III antiarrhythmic drugs, especially sotalol, which may be used orally and for long periods, are a potential therapeutic option for decreasing the defibrillation threshold in ICD/CRT-D patients with an extremely high defibrillation threshold.

**Study limitations**

Our study group was relatively small and included patients with various heart diseases. In addition, although each ECG lead shows similar signal characteristics (30) and we used the lead II on ECG for the frequency analysis, there may be spatial differences in the DF in the whole heart (15). In this study, the frequency analyses were performed using induced VF under general anesthesia, the electrophysiological characteristics of which may differ from those of spontaneous VF (31). The defibrillation threshold is affected by variables of the ICD system, such as the number of defibrillation coils and position of the defibrillation lead and ICD (32-34). However, in the current study, the ICDs and leads were positioned similarly in all patients, and the number of defibrillation coils did not affect the DF or defibrillation threshold. Moreover, we used various models of ICDs and CRT-Ds by several manufacturers in this study, and each model has unique waveform characteristics of the delivered shocks. Therefore, the defibrillation threshold may have been affected by the differences in the waveform of the shocks.

**Conclusion**

We found that the DF of VF is associated with underlying heart disease, the cardiac function, cardiac conduction, ventricular refractoriness and defibrillation threshold. Our findings may be useful for identifying and managing patients with a high defibrillation threshold.

**The authors state that they have no Conflict of Interest (COI).**

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