**Prediction of Lethal Arrhythmic Events Through Remote Monitoring Using Heart Rate Variability Analysis in Patients with an Implantable Cardioverter Defibrillator**

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**Summary**

We prospectively collected device and heart rate data through remote monitoring (RM) of patients with an implantable cardioverter defibrillator (ICD). The objective was to identify the predictors of lethal arrhythmic events (VT/VF).

Thirty-three patients (mean age: 50 years) with ICDs [with functionality of heart rate variability (HRV) analysis] were divided into two groups [VT/VF(+), VT/VF(−)]. Clinical, device (ventricular lead impedance; amplitude of ventricular electrogram), and HRV data were compared between the two groups. The NN interval-index (SDNNi) was calculated for every 5 minutes, and the mean, maximum, minimum, and standard deviation of SDNNi during the 24-hour period were used.

During the observation period of 13 ± 10 months, 10 patients experienced VT/VF events. Total mean, max, and min SDNNi were higher in the VT/VF(+) than the VT/VF(−) group (132.9 ± 9.3 versus 93.5 ± 6.1, $P = 0.0013$; 214.6 ± 10.6 versus 167.0 ± 7.0, $P = 0.0007$; 71.2 ± 7.5 versus 43.9 ± 4.9, $P = 0.0047$). On logistic regression analysis, a total mean SDNNi of 100.1, max SDNNi of 185.0 and min SDNNi of 52.0 as cut-off values for prediction of a VT/VF event demonstrated significant receiver operating characteristic (ROC) curves ($AUC = 0.86$, $P = 0.0007$; $AUC = 0.84$, $P = 0.0005$; $AUC = 0.78$, $P = 0.0030$). The max $\Delta$SDNNi, i.e., difference from baseline SDNNi, and min $\Delta$SDNNi in 7 and 28 days preceding VT/VF events were significant predictors of VT/VF events.

Time-domain HRV analysis through a RM system may help identify patients at high risk of lethal arrhythmic events; in addition, it may help predict the occurrence of lethal arrhythmic events in specific cases.

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**Key words:** Ventricular tachycardia, Ventricular fibrillation, Autonomic nervous system
may help predict the incidence of lethal arrhythmic events in ICD patients.

**Methods**

**Study population:** A total of 44 patients had received an ICD with which continuous RM and time-domain HRV analysis (<5 minutes time resolution) were available (Iforia 7 DR-T, Iforia 7 VR-T, Illesto 5 DR-T, Illesto 7 DR-T, Illesto 7 VR-T DX, Ilivia 7 DR-T, Iperia 7 DR-T, Iperia 7 VR-T DX, Itevria 5 DR-T, and Lumax 740 DR-T, Biotronik SE & Co. KG, Berlin, Germany) between February 2014 and May 2018. The indications for ICD implantation were primary or secondary prevention of arrhythmia and sudden cardiac death. Out of the 44 patients, 6 were excluded due to missing data. Since this study aimed to analyze the clinical characteristics of each patient including age, sex, basic cardiovascular disease, associated diseases, purpose of ICD implantation, main prescription, ECG parameters and UCG parameters were obtained as baseline information (Table I). As device data and parameters, ventricular lead impedance, amplitude of ventricular electrogram, atrial pacing percentage, ventricular pacing percentage and premature ventricular contraction (PVC) counts were obtained once a day through the RM system. For analysis of these two device parameters, the following data were evaluated: 1) total mean data: mean ventricular lead impedance, mean amplitude of ventricular electrogram, mean atrial pacing percentage, ventricular pacing percentage and mean PVC counts for all days during the observation period; 2) maximum value during the observation; 3) minimum value during the observation; and 4) dispersion of data: difference of max and min values during the observation. For each patient, all heart beat data were accumulated and transferred once a day to the server of the RM system. Through the accumulated intracardiac electrograms, sinus beats (detected as N beats) were automatically selected by checking the stability of the intervals in intracardiac electrograms. By using all N-N intervals, i.e., the intervals of normal sinus beats, the mean N-N interval was calculated for every 5 minutes, and the standard deviation of the N-N interval was calculated as the index of time-domain analysis of HRV (SDNNi). The frequency-domain analysis of HRV was not available in ICD through this RM system. Because the main point of this study was to explore useful parameters for the prediction of arrhythmic events through an RM system, unavailable parameters were not included as parameters. The mean of such 5-minute SDNNi was calculated for 24-hour data for each day and was defined as daily SDNNi. For analysis of this daily SDNNi, the following parameters were evaluated: 1) total mean SDNNi: the mean of total daily SDNNi during the observation period; 2) max SDNNi: the maximum
daily SDNNi during the observation period; 3) min SDNNi: the minimum daily SDNNi during the observation period; and 4) dispersion of daily SDNNi: difference of max and min daily SDNNi during the observation period. For patients with lethal arrhythmic events, the mean, max and min of daily SDNNi during the observation period; 3) min SDNNi during the observation period; 4) dispersion of daily SDNNi: the minimum daily SDNNi during the observation period; and 5) SDNNi: the differences of each SDNNi from data pertaining to 28 days without lethal arrhythmic events; and 6) SDNNi: the differences of each SDNNi from data pertaining to the total observation period.

**Grouping and data analysis:** Thirty-three patients were prospectively observed for 3-23 months. VT/VF events were defined as ventricular tachycardia/ventricular fibrillation; IHD, ischemic heart disease; CKD, chronic kidney disease; AAD, Antiarrhythmic drugs; ECG, electrocardiogram; HR, heart rate; UCG, ultrasound echocardiogram; LVDd, left ventricular diastolic diameter; LVDs, left ventricular systolic diameter; IVS, interventricular septum; PW, posterior wall; LVEF, left ventricular ejection fraction; AR, aortic regurgitation; MR, mitral regurgitation; and TR, tricuspid regurgitation. P values show the results of statistical comparison between the VT/VF (+) and VT/VF (−) groups.

**Statistical analysis:** All data are expressed as the mean ± standard deviation, unless otherwise stated. Statistical analysis was performed by one-way analysis of variance or the 2-tailed t-test using JMP statistical software (SAS Institute Inc., Cary, NC, USA). Logistic regression analysis was performed to evaluate the ability of the parameters to predict events and to draw receiver operating characteristic (ROC) curves; P values < 0.05 were considered indicative of statistical significance.

### Table 1. Clinical Characteristics of the Study Population

|                     | Total n = 33 | VT/VF (+) n = 10 | VT/VF (−) n = 23 | P value |
|---------------------|--------------|-----------------|-----------------|---------|
| Age, years          | 50 ± 17      | 37 ± 5          | 56 ± 3          | 0.0030  |
| Male, n (%)         | 29 (88)      | 8 (80)          | 21 (91)         | 0.3605  |
| Basic cardiovascular disease |             |                 |                 |         |
| IHD, n (%)          | 11 (33)      | 1 (10)          | 10 (43)         |         |
| Cardiomyopathy, n (%) | 9 (27)      | 3 (30)          | 6 (26)          |         |
| Brugada syndrome, n (%) | 8 (24)      | 4 (40)          | 4 (17)          | 0.3754  |
| Long QT syndrome, n (%) | 2 (6)       | 1 (10)          | 1 (4)           |         |
| Others, n (%)       | 3 (9)        | 1 (10)          | 2 (9)           |         |
| Complicated disease |             |                 |                 |         |
| Hypertension, n (%) | 9 (27)       | 0 (0)           | 9 (39)          | 0.0204  |
| CKD, n (%)          | 4 (12)       | 0 (0)           | 4 (17)          | 0.1595  |
| Heart Failure (> NYHA II), n (%) | 7 (21)      | 2 (20)          | 5 (22)          | 0.9106  |
| Medication          |             |                 |                 |         |
| β blocker, n (%)    | 18 (55)      | 6 (60)          | 12 (52)         | 0.6782  |
| Class I AAD, n (%)  | 1 (3)        | 0 (0)           | 1 (4)           | 0.5031  |
| Class III AAD, n (%)| 12 (36)      | 4 (40)          | 8 (35)          | 0.7746  |
| ECG parameters      |             |                 |                 |         |
| Basic HR (bpm)      | 66.6 ± 8.7   | 66.6 ± 2.8      | 66.6 ± 1.9      | 0.9956  |
| PR interval (msec)  | 171.0 ± 37.6 | 172.4 ± 12.1    | 170.3 ± 8.3     | 0.8864  |
| QRS duration (msec) | 112.2 ± 20.6 | 104.9 ± 6.4     | 115.7 ± 4.4     | 0.1770  |
| QTc interval (msec) | 40.1 ± 7.2   | 432.2 ± 12.4    | 454.0 ± 8.6     | 0.1593  |
| UCG parameters      |             |                 |                 |         |
| LVDd (mm)           | 49.9 ± 11.0  | 52.2 ± 3.5      | 48.9 ± 2.4      | 0.4488  |
| LVDs (mm)           | 35.4 ± 12.9  | 37.4 ± 4.1      | 34.4 ± 2.9      | 0.5564  |
| IVS (mm)            | 10.0 ± 3.3   | 8.6 ± 1.0       | 10.7 ± 0.7      | 0.0928  |
| PW (mm)             | 9.8 ± 3.0    | 8.7 ± 0.9       | 10.4 ± 0.6      | 0.1330  |
| LVEF (%)            | 53.2 ± 16.2  | 54.2 ± 5.5      | 52.7 ± 3.8      | 0.8279  |
| E/e'                | 12.4 ± 7.0   | 9.2 ± 2.1       | 14.1 ± 1.6      | 0.0706  |
| Δ (cm/sec)          | 8.0 ± 4.4    | 11.1 ± 1.2      | 6.2 ± 0.9       | 0.0024  |
| AR > III (*)        | 0 (0)        | 0 (0)           | 0 (0)           | 0.1407  |
| MR > III (*)        | 1 (3)        | 1 (10)          | 0 (0)           | 0.1407  |
| TR > III (*)        | 1 (3)        | 0 (0)           | 1 (4)           | 0.4603  |

VT/VF indicates ventricular tachycardia/ventricular fibrillation; IHD, ischemic heart disease; CKD, chronic kidney disease; AAD, Antiarrhythmic drugs; ECG, electrocardiogram; HR, heart rate; UCG, ultrasound echocardiogram; LVDd, left ventricular diastolic diameter; LVDs, left ventricular systolic diameter; IVS, interventricular septum; PW, posterior wall; LVEF, left ventricular ejection fraction; AR, aortic regurgitation; MR, mitral regurgitation; and TR, tricuspid regurgitation.

**Remote Monitoring to Predict Lethal Arrhythmia**

In The Heart Journal

**Advance Publication**
Comparison of parameters in VT/VF groups with and without VT/VF, i.e., a VT/VF(+) group, Accordingly, the study population was divided into two groups: VT/VF(+). Of the 10 episodes, 7 were VF and 3 were VT. During the observation period of 13 ± 10 months (median 12), 10 patients experienced VT/VF, i.e., a VT/VF(+) group, and 33 patients experienced VT/VF(−) group. Our study population included 33 patients (2 with VT, 23 with VT/VF(−) and 10 patients experienced VT/VF(+) group). The main cardiovascular disease in 26/33 patients (2 with VT, 23 with VT/VF(−) and 10 patients experienced VT/VF(+) group). The main cardiovascular disease was ischemic heart disease in 33%, cardiomyopathy in 27%, inherited primary arrhythmia, i.e., Brugada or long QT syndrome, in 30%, and others in 9%. A beta-blocker was used in 55% and an antiarrhythmic drug, mainly amiodarone, was prescribed in 39% of the patients. ICDs were implanted for secondary prevention of sudden cardiac death (SCD) in 26/33 patients (2 with VT, and 24 with VF). In the remaining 7 patients, ICDs were implanted for primary prevention of SCD.

**Results**

**Clinical characteristics of patients:** The clinical characteristics of the study population are summarized in Table I. The mean age was 50 ± 17 years; 12% (4/33 patients) were significantly younger (37 ± 5 versus 56 ± 3 years, \( P = 0.0030 \)) and had a significantly lower incidence of hypertension (0 versus 39%, \( P = 0.0204 \)) as compared to those in the VT/VF(−) group. No significant between-group differences were observed with respect to the other parameters. Table II summarizes the accumulated parameters through the RM system in the total study population and in the VT/VF(+) and VT/VF(−) groups. Upon comparing the two groups, no significant between-group differences were observed with respect to cardiac device data (ventricular lead impedance and amplitude of ventricular electrogram) and parameters (atrial pacing percentage, ventricular pacing percentage and PVC counts). In contrast, SDNNi data exhibited significant differences between the two groups. The total mean, max, and min SDNNi in the VT/VF(+) group were significantly higher than those in the VT/VF(−) group. However, no significant between-group difference was observed with respect to the dispersion of SDNNi.

**Time course change in SDNNi before the lethal arrhythmic events:** To evaluate the time course change in SDNNi data before the lethal arrhythmic events, we evaluated the total mean, maximum, and minimum SDNNi in the 7 and 28 days preceding the lethal arrhythmic events for each patient in the VT/VF(+) group. The max and min were significantly lower (37 ± 5 versus 56 ± 3 years, \( P = 0.0030 \)) and had a significantly lower incidence of hypertension (0 versus 39%, \( P = 0.0204 \)) as compared to those in the VT/VF(−) group. No significant between-group differences were observed with respect to the other parameters. Table II summarizes the accumulated parameters through the RM system in the total study population and in the VT/VF(+) and VT/VF(−) groups. Upon comparing the two groups, no significant between-group differences were observed with respect to cardiac device data (ventricular lead impedance and amplitude of ventricular electrogram) and parameters (atrial pacing percentage, ventricular pacing percentage and PVC counts). In contrast, SDNNi data exhibited significant differences between the two groups. The total mean, max, and min SDNNi in the VT/VF(+) group were significantly higher than those in the VT/VF(−) group. However, no significant between-group difference was observed with respect to the dispersion of SDNNi.

**Comparison of parameters in VT/VF(+) and VT/VF(−) groups:** Table I shows the clinical characteristics of patients in the two groups. Patients in the VT/VF(+) group were significantly younger (37 ± 5 versus 56 ± 3 years, \( P = 0.0030 \)) and had a significantly lower incidence of hypertension (0 versus 39%, \( P = 0.0204 \)) as compared to those in the VT/VF(−) group. No significant between-group differences were observed with respect to the other parameters. Table II summarizes the accumulated parameters through the RM system in the total study population and in the VT/VF(+) and VT/VF(−) groups. Upon comparing the two groups, no significant between-group differences were observed with respect to cardiac device data (ventricular lead impedance and amplitude of ventricular electrogram) and parameters (atrial pacing percentage, ventricular pacing percentage and PVC counts). In contrast, SDNNi data exhibited significant differences between the two groups. The total mean, max, and min SDNNi in the VT/VF(+) group were significantly higher than those in the VT/VF(−) group. However, no significant between-group difference was observed with respect to the dispersion of SDNNi.

**Table II. Comparison of Accumulated Parameters through RM System**

| Parameter                                | Total (n = 33) | VT/VF (+) (n = 10) | VT/VF (−) (n = 23) | \( P \) value |
|------------------------------------------|----------------|--------------------|--------------------|--------------|
| **Atrial pacing percentage (%)**         |                |                    |                    |              |
| Total mean                               | 19.3 ± 27.5    | 19.9 ± 12.6        | 19.1 ± 7.3         | 0.9579       |
| Maximum                                  | 42.0 ± 41.2    | 52.8 ± 18.7        | 38.3 ± 10.8        | 0.5117       |
| Minimum                                  | 2.1 ± 8.0      | 0.8 ± 3.7          | 2.5 ± 2.1          | 0.6995       |
| Difference of max and min                | 39.9 ± 39.1    | 52.0 ± 17.7        | 35.9 ± 10.2        | 0.4391       |
| **Ventricular pacing percentage (%)**    |                |                    |                    |              |
| Total mean                               | 5.0 ± 10.5     | 7.7 ± 3.3          | 3.8 ± 2.2          | 0.3263       |
| Maximum                                  | 15.9 ± 28.9    | 18.8 ± 9.3         | 14.5 ± 6.2         | 0.7060       |
| Minimum                                  | 0.0 ± 0.2      | 0.0 ± 0.1          | 0.0 ± 0.0          | 0.5091       |
| Difference of max and min                | 15.8 ± 28.8    | 18.8 ± 9.2         | 14.5 ± 6.2         | 0.7023       |
| **PVC (counts/hour)**                    |                |                    |                    |              |
| Total mean                               | 19.2 ± 27.9    | 12.9 ± 8.9         | 22.1 ± 6.0         | 0.3979       |
| Maximum                                  | 296.8 ± 826.8  | 200.5 ± 264.9      | 340.5 ± 178.6      | 0.6643       |
| Minimum                                  | 0.7 ± 1.7      | 0.4 ± 0.6          | 0.8 ± 0.4          | 0.5815       |
| Difference of max and min                | 70.2 ± 417.3   | 200.1 ± 264.9      | 339.8 ± 178.6      | 0.6651       |
| **Amplitude of right ventricular electrogram (mV)** |              |                    |                    |              |
| Total mean                               | 13.3 ± 4.7     | 14.3 ± 1.5         | 12.9 ± 1.0         | 0.4421       |
| Maximum                                  | 15.5 ± 4.3     | 16.3 ± 1.4         | 15.2 ± 0.9         | 0.5183       |
| Minimum                                  | 10.9 ± 4.6     | 11.9 ± 1.5         | 10.5 ± 1.0         | 0.4548       |
| Difference of max and min                | 4.6 ± 2.1      | 4.4 ± 0.7          | 4.6 ± 0.5          | 0.7537       |
| **SDNNi (msec)**                         |                |                    |                    |              |
| Total mean                               | 105.5 ± 34.3   | 132.9 ± 9.3        | 93.5 ± 6.1         | 0.0013       |
| Maximum                                  | 181.4 ± 39.7   | 214.6 ± 10.6       | 167.0 ± 7.0        | 0.0007       |
| Minimum                                  | 52.2 ± 26.6    | 71.2 ± 7.5         | 43.9 ± 4.9         | 0.0047       |
| Difference of max and min                | 129.3 ± 32.6   | 143.4 ± 20.0       | 123.1 ± 6.6        | 0.1019       |

VT/VF indicates ventricular tachycardia/ventricular fibrillation; PVC, premature ventricular contraction; and SDNNi, standard deviation of NN intervals-index. \( P \) values show the results of statistical comparison between the VT/VF(+) and VT/VF(−) groups.
Figure 2. ROC curves for the total mean, maximum and minimum SDNNi in the VT/VF (+) group during observation period. A: ROC curve of total mean SDNNi: Use of mean SDNNi of 100.1 as the threshold for prediction of lethal arrhythmic events was associated with 100% sensitivity and 65% specificity (AUC 0.86, P = 0.0007). B: ROC curve of max SDNNi: Use of maximum SDNNi of 185.0 as the threshold for prediction of lethal arrhythmic events was associated with 90% sensitivity and 74% specificity (AUC 0.84, P = 0.0005). C: ROC curve of min SDNNi: Use of minimum SDNNi of 52.0 as the threshold for prediction of lethal arrhythmic events was associated with 80% sensitivity and 70% specificity (AUC 0.78, P = 0.0030). ROC indicates receiver operating characteristic; and AUC, area under the curve.

$\Delta$SDNNi exhibited time course changes in the period preceding the arrhythmic events (Table III). The max $\Delta$SDNNi significantly decreased in the 7 days preceding the lethal arrhythmic event, while the min $\Delta$SDNNi significantly increased in the 7 and 28 days preceding the lethal arrhythmic events. However, the total mean $\Delta$SDNNi did not exhibit any time course changes in the period preceding the arrhythmic events. Although there is no rational to choose 7 and 28 days as data sampling periods, we employed these periods for data sampling through our own pilot analysis. Because 2-3 days or less before the VT/VF event was too close to the actual events and not realistic to obtain them through RM system, we did not employ such a short period.

Evaluation of SDNNi data as the predictor for VT/VF events: In the logistic regression analysis, ROC curves were drawn for the following parameters to assess their predictive ability for VT/VF: 1) total mean SDNNi, max, and min SDNNi during the total observation period; and 2) max $\Delta$SDNNi and min $\Delta$SDNNi in the 7 days preceding the lethal arrhythmic events. Figure 2 exhibits the 3 ROC curves for these predictors. Each of the parameters showed a significant predictive ability. ROC curve analysis of total mean SDNNi revealed the optimal cut-off
value of 100.1 was associated with 100% sensitivity and 65% specificity for predicting a VT/VF event (AUC: 0.86; $P = 0.0007$) (Figure 2A). On ROC curve analysis of max SDNNi, the optimal cut-off value of 185.0 was associated with 90% sensitivity and 74% specificity for predicting a VT/VF event (AUC: 0.84; $P = 0.0005$) (Figure 2B). ROC curve analysis of min SDNNi showed the optimal cut-off value of 52.0 was associated with 80% sensitivity and 70% specificity for predicting a VT/VF event (AUC: 0.78; $P = 0.0030$) (Figure 2C). Figure 3 presents 2 ROC curves using ΔSDNNi data pertaining to 7 days preceding the lethal arrhythmic events as predictors. The max ΔSDNNi, i.e., difference from baseline SDNNi, and min ΔSDNNi in the 7 and 28 days preceding the arrhythmic events exhibited time course changes in comparison with baseline values. These were found to be significant predictors of lethal arrhythmic events with optimal cut-off values of 46.8 for max ΔSDNNi and −42.4 for min ΔSDNNi for 7 day data (AUC = 0.91, $P = 0.0002$ and AUC = 0.88, $P = 0.0014$) (Figure 3A, B). The min ΔSDNNi for 28 day data did not exhibit time course changes in comparison with baseline values (AUC = 0.74, $P = 0.0842$).

**Discussion**

This study revealed several interesting findings pertaining to SDNNi obtained through RM of implantable defibrillation devices. First, the total mean, max, and min SDNNi in the VT/VF(+) group were significantly higher than those in the VT/VF(−) group. Second, ROC curve analysis revealed a significant predictive ability of these parameters for lethal arrhythmic events (optimal cut-off values: 100.1 for mean, 185.0 for max and 52.0 for min SDNNi). Third, on comparing the time course changes in SDNNi data within the VT/VF(+) group, the max ΔSDNNi in the 7 days preceding the arrhythmic events was lower than the baseline value, and the min ΔSDNNi in the 7 and 28 days preceding the arrhythmic events were higher than the baseline value. Finally, the ΔSDNNi data also showed a significant predictive ability for lethal arrhythmic events on ROC curve analysis (optimal cut-off values: −42.4 for increase in min ΔSDNNi and 46.8 for decrease in max ΔSDNNi in the 7 days preceding the arrhythmic events).

**Autonomic nervous system and lethal arrhythmia:** Previous studies have demonstrated that most of the HRV parameters reflect accelerated sympathetic activity, reduced parasympathetic activity, or both.9) Particularly, time-domain parameters of HRV, i.e., SDANN (standard deviation of the normal-normal R-R period), rMSSD (root-mean-square of successive differences), or pNN50 (percentage of successive NN intervals differing by > 50.0 ms), as well as HF (high frequency) power of frequency-domain HRV parameter are believed to reflect parasympathetic activity.10,11) Although the physiological meaning and/or the precise mechanism of modifying SDNNi are not well understood, SDNNi clearly reflects systemic autonomic nervous activity.12) Figure 4 shows the current...
understanding of the relationship between autonomic nervous activity and the occurrence of arrhythmias. Enhanced automaticity, triggered activity and reentry are known to be exaggerated by enhanced sympathetic tone and these may result in lethal arrhythmias in various situations. Although the actual occurrence of lethal arrhythmias depends on various factors, several studies have emphasized the involvement of enhanced or changing autonomic nervous activity.\textsuperscript{13-17} Several studies have revealed the relationship between HRV parameters and increases in lethal arrhythmias in patients with implanted ICDs.\textsuperscript{18,19} Lown and Verrier\textsuperscript{13} demonstrated that enhanced sympathetic activity may decrease the threshold for induction of VF. In contrast, parasympathetic activity increases the activation threshold of myocardium and suppresses lethal arrhythmias.\textsuperscript{13,17} Therefore, upregulation of sympathetic activity and/or downregulation of parasympathetic activity are risk factors for lethal arrhythmias and may adversely affect the ventricular arrhythmogenic substrate.\textsuperscript{16} Interestingly, apart from the enhancement or suppression of individual systems, the interrelationship between the two systems plays a more important role in inducing lethal arrhythmias. Although the precise physiological mechanism remains unclear in each specific condition, imbalance or rapid changes in autonomic activity may be associated with electrical instability and lethal arrhythmias.\textsuperscript{16,23}

**HRV and lethal arrhythmia:** Most previous studies have demonstrated a relationship between frequency-domain analysis of HRV and lethal arrhythmias in the minutes to hours preceding VT/VF in patients exhibiting these arrhythmias during Holter ECG recordings. Lombardi, \textit{et al.}\textsuperscript{24} and Pruvot, \textit{et al.}\textsuperscript{25} have documented alterations of frequency-domain parameters of HRV in the minutes preceding the occurrence of lethal arrhythmias. These reports emphasize the importance of temporal surge in the LF/HF value (i.e., sympathetic activity) as well as temporal suppression of the HF value (i.e., parasympathetic activity) in the period immediately preceding the arrhythmic events. However, these signs are too close to the actual events; therefore, it is difficult to use these as predictors of arrhythmic events. Additionally, frequency-domain analysis has a methodological limitation in cases with frequent extrasystoles. Since frequency-domain analysis involves analysis of the R-R intervals in sinus rhythm, the method is not applicable to patients with frequent PVCs. In contrast, although time-domain analysis is also liable to be influenced by extrasystoles, this influence is limited in comparison with frequency-domain analysis. In the present study, we utilized RM of implanted devices, i.e., ICD, for long-term time-domain analysis in patients at risk of lethal arrhythmias. SDNNi, the parameter of time-domain analysis of HRV, exhibited a significant difference between patients with and without lethal arrhythmic events. Additionally, SDNNi exhibited time course changes, i.e., a decrease in max SDNNi and increase in min SDNNi in the period preceding the arrhythmic events. To the best of our knowledge, this is the first systematic study that demonstrates the relationship between lethal arrhythmias and the time-domain analysis parameter of HRV using RM of ICD. On the other hand, the cardiac device data (ventricular lead impedance and amplitude of ventricular electrogram) and parameters (atrial pacing percentage, ventricular pacing percentage and PVC counts) did not show significant differences between patients with and without lethal arrhythmic events. This may indicate that the occurrence of lethal arrhythmia is more likely to be associated with changes in parameters of autonomic activity in comparison with the electrophysiological parameters of myocardium.

**Underlying mechanism of the predictive value of**
SDNNi for VT/VF: Because time-domain analysis parameters of HRV reflect both sympathetic and parasympathetic activity, these could not be separated in the analysis. However, our results clearly indicate the importance of overall trends of SDNNi data to discriminate patients at higher risk of lethal arrhythmic events. Additionally, not a temporal but gradual time course change in SDNNi was associated with lethal arrhythmic events in patients with VT/VF events. The mechanisms of these findings are not clear, however, larger SDNNi possibly reflects a greater change in autonomic activity which may increase the risk of lethal arrhythmias in at-risk patients. However, the time course change in SDNNi in cases with VT/VF events is quite interesting. The mean SDNNi itself was unchanged; however, there was an increase in min SDNNi and decrease in max SDNNi, which reduced the range of variation of SDNNi. We understand that changes in maximum and minimum ΔSDNNi with unchanged total mean ΔSDNNi would indicate the changes in the range of oscillation of ΔSDNNi. We speculate that such a change in oscillation would reflect instability of autonomic tone, but direct evidence should be evaluated in a different style of study. Because mean SDNNi in patients with VT/VF events was basically higher than that in patients without VT/VF events, the autonomic tone may converge to a higher level prior to the occurrence of an arrhythmic event. The precise mechanism of this phenomenon should be evaluated by using other methods, such as simultaneous frequency-domain analysis of HRV; this analysis was not possible in the present study.

Limitations: Several limitations of this study should be considered while interpreting the results. First, this study was a single-center study with a small sample size. It did not allow us to perform subgroup analysis with different types of basic cardiovascular diseases. This happened because we limited the study population to patients with a specific type of ICD in which real-time time-domain analysis of HRV was available through an RM system. Although we think we can still derive the importance of HRV analysis through the RM system in this study, re-evaluation of such analysis will be necessary in larger populations in future studies. Second, HRV itself cannot be analyzed in patients with sinus node dysfunction, abnormal atrioventricular conduction, AF/flutter, atrial tachycardia, or cardiac pacemakers. Finally, because this study was just a short-term prospective observation, our results may not completely reflect the prediction of lethal arrhythmic events over the long term. These points should be resolved in a long-term prospective study with a larger study population.

Conclusions

Time-domain analysis of HRV through an RM system may help identify patients who are at a higher risk of arrhythmic events; in addition, it may help predict the occurrence of lethal arrhythmic events in specific cases.

Disclosure

Conflicts of interest: This study received no financial support from commercial sources, and the authors state there are no conflicts of interest. No specific unapproved use of any compound or product occurred.

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