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Original Article

The effects of nifekalant hydrochloride on the spatial dispersion of repolarization after direct current defibrillation in patients with oral amiodarone and β-blocker therapy

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ABSTRACT

Background: Although nifekalant hydrochloride (NIF) has been demonstrated to suppress ventricular tachyarrhythmias, especially electrical storms, the mechanism by which it does so is still unclear. We examined the effects of NIF on the spatial dispersion of repolarization (SDR) after implantable cardioverter-defibrillator (ICD) shock.

Methods and Results: In 35 patients with oral amiodarone and β-blocker therapy, and an ICD, we recorded the 87-lead electrocardiogram during sinus rhythm (CONTROL-1 group) under general anesthesia, and just after the termination of induced ventricular fibrillation (VF) by ICD shock, with or without NIF administration. In all recordings, the corrected QT interval (QTc) was measured in each lead. The dispersion of QTc (QTc-D; maximum QTc minus minimum QTc) was also measured. Compared with that in the CONTROL-1 group, the QTc-D exhibited significant deterioration after ICD shock (61 ± 14 and 90 ± 19 $ms^{1/2}$, respectively; $p < 0.05$). However, after the termination of induced VF by ICD shock with NIF administration, the QTc-D did not differ significantly from that in the CONTROL-1 group (63 ± 20 and 61 ± 14 $ms^{1/2}$, respectively).

Conclusions: NIF suppressed the deterioration of the SDR after ICD shock. This might be one of the mechanisms by which NIF suppresses recurrence of ventricular tachyarrhythmia just after ICD shock in patients with oral amiodarone and β-blocker therapy.

1. Introduction

The implantable cardioverter-defibrillator (ICD) has dramatically reduced the risk of sudden death in patients with malignant ventricular tachyarrhythmias [1,2]. However, 10–30% of patients who have undergone ICD implantation experience "electrical storms," in which ventricular tachyarrhythmias occur ≥2 times within a 24-h period [3]. Patients with severe electrical storm are known to have a worse prognosis [4].

Some studies have demonstrated that ICD shocks increase the dispersion of ventricular repolarization [5,6]. The spatial dispersion of ventricular repolarization plays a role in the initiation and maintenance of malignant ventricular tachyarrhythmias, including electrical storms. The QT dispersion and recovery time dispersion are assumed to reflect the spatial heterogeneity [7,8].

Few therapeutic options are currently available for controlling electrical storms. Nifekalant hydrochloride (NIF) is a class III antiarrhythmic drug that causes dose-dependent prolongation of the action potential duration in both atrial and ventricular muscle, mainly by reducing the rapid component of the delayed rectifier K^+ current (I_{kr}) [9,10]. Several clinical studies have demonstrated the effectiveness of intravenous NIF for recurrent ventricular tachyarrhythmias that are resistant to other antiarrhythmic drugs and ICD shock [11], especially electrical storms [12]. However, little is known about the electropharmacological basis of the efficacy of NIF in treating these arrhythmias. Moreover, the effect of NIF on the spatial dispersion of repolarization (SDR) has not been reported yet in any clinical study.

In the clinical setting, most patients with electrical storm and impaired left ventricular function because of structural heart diseases take oral amiodarone and β-blocker agents. Therefore, in the present study, we measured the SDR obtained from the 87-lead body surface-mapping electrocardiogram (ECG), and examined the effects of NIF on the SDR after ICD shock in patients with oral amiodarone and β-blocker therapy.

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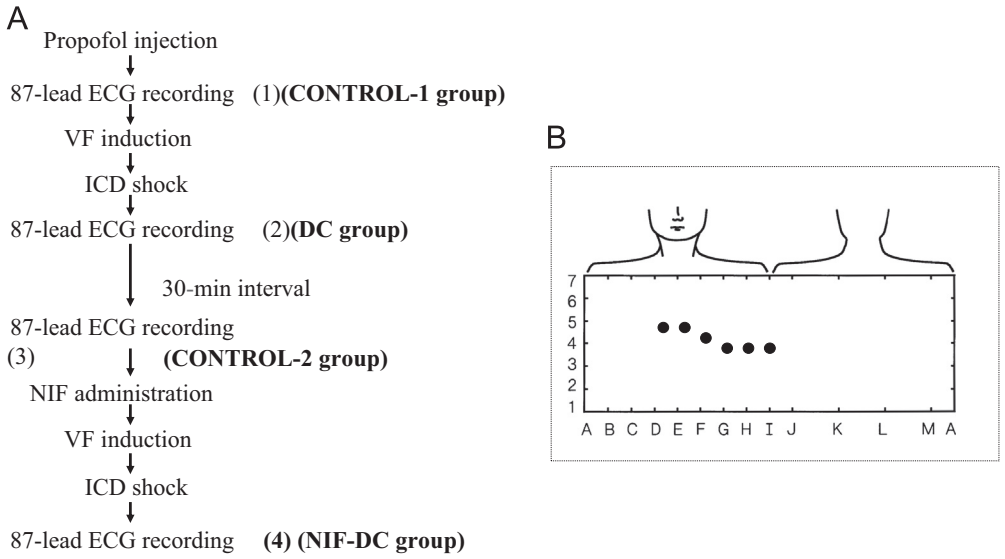

Fig. 1. (A) Protocol of this study. The 87-lead body surface ECG was recorded 4 times in all patients [(1)–(4)]: (1) CONTROL-1 group, during sinus rhythm after injection of propofol; (2) DC group, just after termination of induced VF by ICD shock; (3) CONTROL-2 group, 30 min after ICD shock, before administration of NIF; (4) NIF-DC group, just after termination of induced VF, after NIF administration by ICD shock. VF, ventricular fibrillation; ICD, implantable cardioverter-defibrillator; NIF, nifekalant hydrochloride. (B) Plots of the 87 unipolar electrode sites and of the 6 precordial leads (dots). The 87 leads are arranged in a lattice-like pattern, with the exception of 4 leads on both midaxillary lines (A6, A7, I6, and I7). Leads V1 and V2 of the 12-lead ECG are located between rows 4 and 5 and columns D and E, and between rows 4 and 5 and columns E and F, respectively, whereas leads V4, V5, and V6 are coincident with G4, H4, and I4, respectively.

Table 1
Patient characteristics.

Men/women (*n*)	28/7
Age (years)	65 ± 9
LVEF (%)	36 ± 14
Underlying heart disease, *n* (%)	
Prior MI	15 (43%)
DCM	6 (17%)
HCM	6 (17%)
Sarcoidosis	4 (11%)
HHD	2 (6%)
Valve disease	2 (6%)
Medication, *n* (%)	
Amiodarone+ β-blocker	35 (100%)

LVEF, left ventricular ejection fraction; MI, myocardial infarction; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HHD, hypertensive heart disease.

Table 2
Measurements of electrocardiographic parameters in 87-lead ECG.

	CONTROL-1	DC	CONTROL-2	NIF-DC
HR (bpm)	61 ± 10	58 ± 10	58 ± 11	51 ± 7
QRS (ms)				
Max	142 ± 43	137 ± 24	138 ± 24	136 ± 23
Min	84 ± 20	81 ± 19	88 ± 21	84 ± 19
QT (ms)				
Max	492 ± 47	524 ± 44[a]	501 ± 40[b]	561 ± 46[a,b,c]
Min	438 ± 55	434 ± 41	455 ± 42	491 ± 45[a,b,c]
QTc ($ms^{1/2}$)				
Max	497 ± 36	511 ± 44	488 ± 34	513 ± 34[c]
Min	443 ± 36	416 ± 39[a]	435 ± 28	454 ± 28[b]
Dispersion				
QRS	62 ± 41	58 ± 10	52 ± 9	53 ± 11
QT	58 ± 8	93 ± 25[a]	53 ± 11[b]	64 ± 17[b]
QTc	61 ± 14	90 ± 19[a]	59 ± 14[b]	63 ± 20[b]

Values are mean ± SD; max, maximum value among the 87 leads; min, minimum value among the 87 leads; Dispersion, max minus min; QT, QT interval; QTc, corrected QT interval.

[a] $p < 0.05$ vs. CONTROL-1;
[b] $p < 0.05$ vs. DC;
[c] $p < 0.001$ vs. CONTROL-2.

2. Methods

2.1. Patient population

A total of 35 consecutive patients (28 men and 7 women, mean age 66 ± 7 years) were enrolled in this study between November 2001 and November 2010. All patients underwent ICD implantation and met all of the following criteria: (1) with structural heart disease except for arrhythmogenic right ventricular cardiomyopathy; (2) with clinical documentation of ventricular tachyarrhythmias or unexplained syncope; and (3) with inducible sustained ventricular tachyarrhythmias during the electrophysiological study and receiving antiarrhythmic drugs. Patients were excluded if they had atrial fibrillation, pacing rhythm, or bundle branch block. In all patients, predischarge testing of the ICD was performed 1 week after implantation. This study was approved by the ethical review committee of our institution. Written informed consent for participation in this study was obtained from all patients.

2.2. Protocol for ICD testing

The protocol for the ICD testing in this study is presented in Fig. 1A.

In all patients, ICD testing was performed under intravenous general anesthesia (propofol), and ventricular fibrillation (VF) was induced using a right ventricular ICD lead. After 8 pacing cycles with a cycle length of 400 ms, an electrical shock of 1.2 J was applied on the top of the T wave. Attempts were made to terminate episodes of induced VF with the ICD with a 20 J biphasic shock. After a 30-min interval, NIF was administered as a loading infusion of 0.3 mg/kg for 10 min. VF was then induced using the same protocol, and termination of VF was attempted with a 20 J biphasic shock. All induced episodes of VF were successfully terminated by a 20 J biphasic shock.

The 87-lead body surface ECG was recorded between the propofol injection and the VF induction as a baseline record (CONTROL-1 group), just after the ICD shock (DC group), 30 min after the ICD shock and before NIF administration (CONTROL-2 group), and just after the ICD shock with a loading infusion of NIF (NIF-DC group).

2.3. Eighty-seven-lead body surface ECG

In all patients, we recorded the 87-lead body surface ECGs in the supine position, using a VCM-3000 (Fukuda Denshi, Tokyo, Japan) [13], in which the leads covered the entire thoracic surface and were arranged in a lattice-like pattern (13×7 matrix), except for 4 leads on the midaxillary lines; 59 leads were located on the anterior chest (columns A–I) and 28 leads on the back (columns J–M) (Fig. 1B). These 87 unipolar ECGs with Wilson's central terminal as a reference; the standard 12-lead ECG; and the Frank X, Y, and Z scalar leads were simultaneously recorded during sinus rhythm.

2.4. Measurements

We visually measured the following parameters in each lead: the QT interval (QT), defined as the time interval between QRS onset and the point at which the isoelectric line intersected a tangential line drawn at the maximal downslope of the positive T-wave or at the maximal upslope of the negative T-wave. The QT was measured from all 87-lead ECGs, and corrected for the R–R interval by using Bazett's method (QTc [corrected QT]: $QT/\sqrt{RR}$). When the peak or nadir of the T wave for a lead could not be detected, that lead was excluded from analysis.

The maximum (max) and minimum (min) QTc values were also obtained from all 87 leads. As an index of SDR, dispersion of QTc (QTc-D) was defined as the interval between the max and min (max minus min) QTc. These measurements were made by 3 cardiologists who were unaware of the clinical findings in the subjects. When the measured values were not identical, the mean values of the 3 measurements were calculated. Intra-observer variability was determined from triplicate measurements.

2.5. Definition of recurrent ventricular tachyarrhythmias

Patients were prospectively followed during the study period. We defined recurrent arrhythmias as sustained ventricular tachyarrhythmia or VF obtained from the ICD memory. Sustained ventricular tachyarrhythmia was defined as a rate of >150 beats/min and treated by ICD using anti-tachycardia pacing or shock therapy. VF was defined as tachyarrhythmia with a rate of >200 beats/min and treated by ICD shock therapy.

2.6. Statistical analysis

Values are mean $\pm$ SD. Differences in each parameter between the CONTROL-1, DC, CONTROL-2, and NIF-DC groups were examined by ANOVA with repeated measures, followed by Scheffé's multiple comparison test. The Mann-Whitney *U*-test was used to compare parameters between 2 factors. Values of $p < 0.05$ were considered significant.

Inter-observer and intra-observer variabilities were assessed according to the Bland and Altman method. Values of $p < 0.05$ were taken to indicate significant differences.

3. Results

3.1. Clinical profile of patients

The characteristics of the patients in this study are presented in Table 1. The mean left ventricular ejection fraction was relatively low (36 ± 14%). Fifteen patients (43%) had prior myocardial infarction, whereas the others (57%) had nonischemic heart disease. All patients were receiving oral amiodarone at a dose of 200 mg/day and β-blocker agents.

3.2. Eighty-seven-lead ECG findings

Each ECG parameter was measured in all 37 patients. Representative ECGs are shown in Figs. 2 and 3. Fig. 2 shows the 87-lead ECG results in the CONTROL-1 group. Fig. 3 shows representative ECGs for the max and min QTc in the CONTROL-1 group (3A), DC group (3B), CONTROL-2 group (3C), and NIF-DC group (3D),

Table 3
Comparison of QTc-D between IHD and non-IHD.

	IHD	Non-IHD
n (%)	15 (43)	20 (57)
CONTROL-1 ($ms^{1/2}$)	62 ± 14	61 ± 8
DC ($ms^{1/2}$)	86 ± 22	94 ± 25
CONTROL-2 ($ms^{1/2}$)	60 ± 9	56 ± 15
NIF-DC ($ms^{1/2}$)	63 ± 20	65 ± 15
$\Delta QTc\text{-}D_{(DC\text{–}CONTROL\text{-}1)}$ ($ms^{1/2}$)	27 ± 19	32 ± 27
$\Delta QTc\text{-}D_{(DC\text{–}NIF\text{-}DC)}$ ($ms^{1/2}$)	26 ± 16	28 ± 21

Values are mean $\pm$ SD.
IHD, ischemic heart disease; non-IHD, nonischemic heart disease.
$\Delta QTc\text{-}D_{(DC\text{-}CONTROL\text{-}1)}$ = the difference of QTc-D between the DC and CONTROL-1 groups.
$\Delta QTc\text{-}D_{(DC\text{–}NIF\text{-}DC)}$ = the difference of QTc-D between the DC and NIF-DC groups.

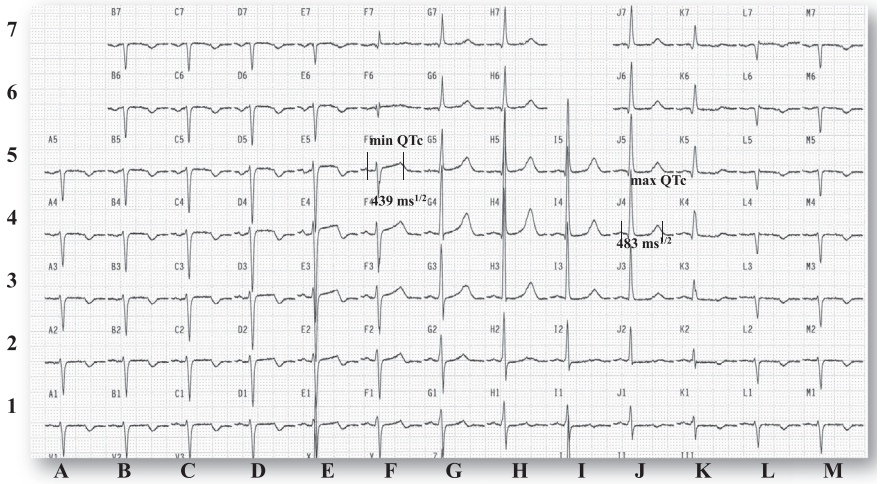

Fig. 2. Representative 87-lead ECG obtained in the CONTROL-1 group. The maximal QTc (max QTc) was located in the left back (J4), and the minimal QTc (min QTc) in the left anterior chest (F5). The QTc-D was 44 $ms^{1/2}$. QTc, corrected QT interval; QTc-D, dispersion of QTc.

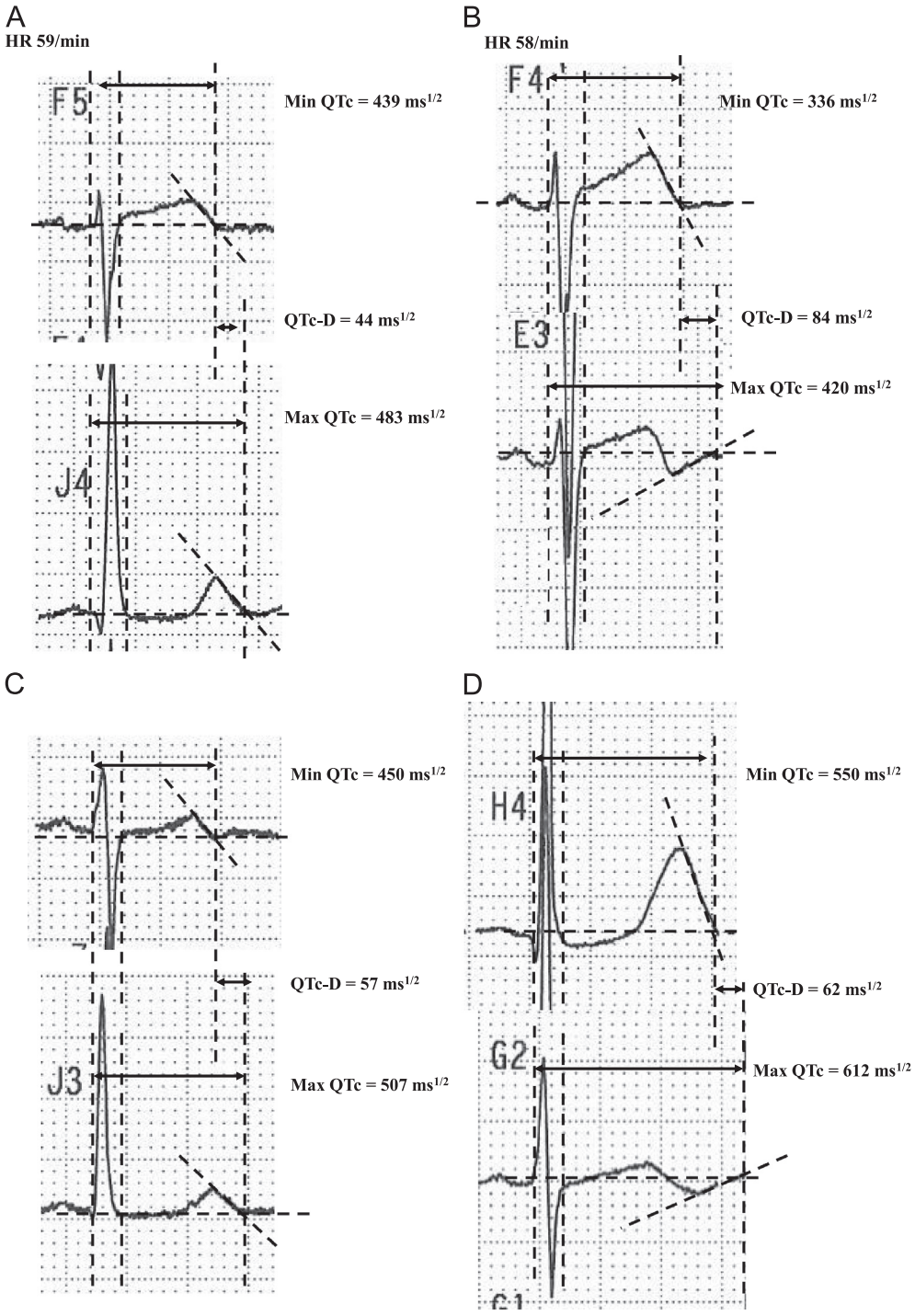

Fig. 3. Representative ECGs in the same patient are shown in each panel. (A) In the CONTROL-1 group, the max QTc, min QTc, and QTc-D were 483 $ms^{1/2}$, 439 $ms^{1/2}$, and 44 $ms^{1/2}$, respectively. (B) After ICD shock, the QTc-D was increased (84 $ms^{1/2}$). (C) In the CONTROL-2 group, the max QTc, min QTc, and QTc-D were 507 $ms^{1/2}$, 450 $ms^{1/2}$, and 57 $ms^{1/2}$, respectively. (D) After nifekalant administration, the max and min QTc were moderately prolonged in the NIF-DC group (612 and 550 $ms^{1/2}$, respectively). In particular, the min QTc in the NIF-DC group was significantly prolonged compared with that in the DC group. Abbreviations are as in Figs. 1 and 2.

for the same patient. Table 2 summarizes each ECG parameter in all patients. Heart rate was significantly decreased after NIF administration. The QRS duration did not differ among all groups.

Table 2 shows that there were no significant differences between the CONTROL-1 and CONTROL-2 groups in all parameters. Compared with the CONTROL-1 and CONTROL-2 groups (497 ± 36 and 488 ± 34 $ms^{1/2}$), the max QTc was not different in the DC group (511 ± 44 $ms^{1/2}$) but was significantly prolonged in the NIF-DC group (513 ± 34 $ms^{1/2}$; $p < 0.001$) (Fig. 4A). On the other hand, the min QTc was significantly shortened in the DC group compared with that in the CONTROL-1 group (416 ± 39 and 443 ± 36 $ms^{1/2}$, respectively; $p < 0.05$). Moreover, the min QTc in the NIF-DC group was significantly prolonged compared with that in the DC group (454 ± 28 and 416 ± 39 $ms^{1/2}$, respectively; $p < 0.05$) (Fig. 4B). Thus, the QTc-D in the DC group was significantly increased compared with those in the CONTROL-1, CONTROL-2, and NIF-DC groups (90 ± 19, 61 ± 14, 59 ± 14, and 63 ± 20 $ms^{1/2}$, respectively; $p < 0.05$) (Fig. 4C).

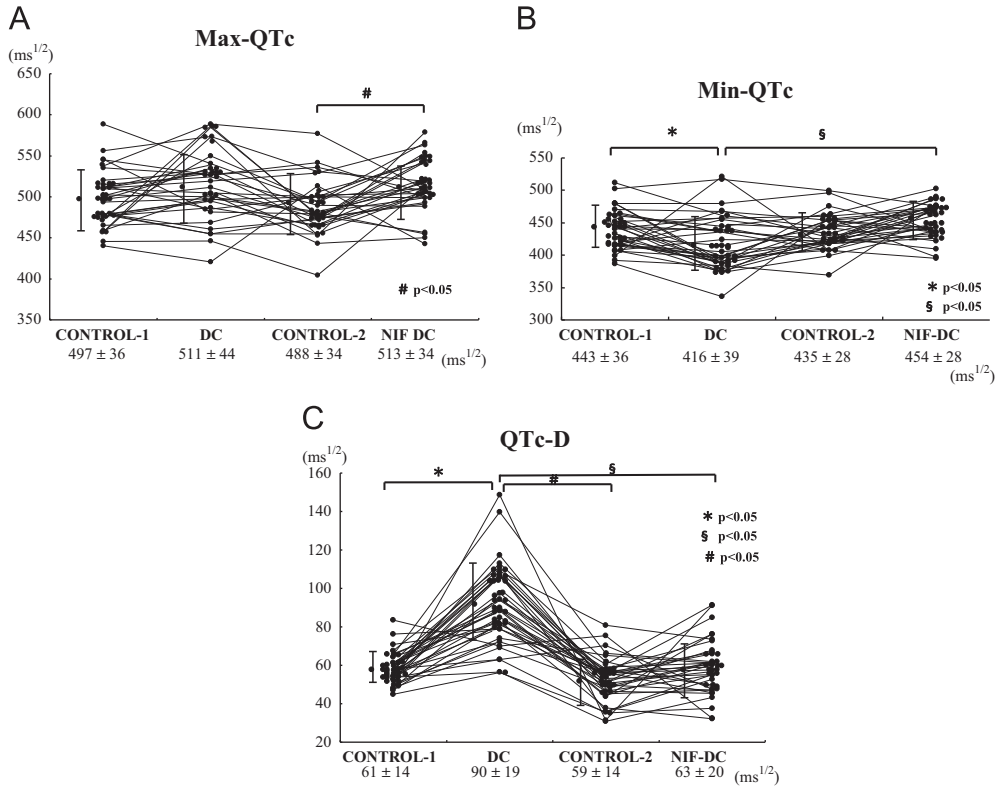

Fig. 4. Comparison of differences between the CONTROL-1, DC, CONTROL-2, and NIF-DC groups in max QTc (A), min QTc (B), and QTc-D (C). Max QTc was mildly prolonged in the NIF-DC group, although it was not significantly different from that in the DC group (A), whereas the min QTc in the DC group was significantly shortened compared with those in the CONTROL-1 and NIF-DC groups (B). Therefore, QTc-D was significantly increased in the DC group compared with that in the NIFE-DC group (C). Other abbreviations are as in Fig. 2.

3.3. Comparison of the effects of SDR between ischemic and nonischemic heart diseases

Table 3 summarizes the comparison of the QTc-D in patients with ischemic heart disease (IHD) or those with nonischemic heart disease (non-IHD). There were no significant differences in any parameter between IHD and non-IHD patients. Concerning the differences in the QTc-D between the DC and CONTROL groups (ΔQTc-$D_{(DC-CONTROL-1)}$), and between the DC and NIF-DC groups (ΔQTc-$D_{(DC-NIF-DC)}$), there were no significant differences between IHD and non-IHD patients. Fig. 5 shows the location of the max QTc and min QTc in the 87 leads in each group. We divided the whole chest surface into 14 areas (Fig. 5A): right lateral (columns A and B, superior [rows 6 and 7], middle [rows 4 and 5], and inferior [rows 1–3]), right anterior (columns C and D, superior, middle, and inferior), left anterior (columns E–G, superior, middle, and inferior), left lateral (columns H and I, superior, middle, and inferior), left posterior (columns J and K), and right posterior (columns L and M). Concerning non-IHD patients, in the CONTROL group (Fig. 5B), the max QTc and min QTc were widely located. In the DC group (Fig. 5C), the location of the max QTc and min QTc became the left anterior and left lateral regions. In the NIF-DC group (Fig. 5D), the distribution of max QTc and min QTc became closer than that in the DC group. Concerning IHD patients, in the CONTROL group, the max QTc was mainly located in the left anterior, left lateral, and posterior regions. The min QTc was mainly located in the anterior region. In the DC group, the location of the max QTc was concentrated on the left anterior and left lateral regions (middle to superior region). The location of the min QTc spread to the inferior and right lateral regions. In the NIF-DC group, the location of the max QTc and min QTc became closer compared with the DC group.

In patients with IHD, we could find no relation between the infarction area and QTc-D.

3.4. Relation between dispersion of repolarization and recurrence of ventricular tachyarrhythmias

During the study period, ventricular tachyarrhythmias occurred in 12 of 35 (34%) patients. Five patients (14%) developed electrical storm. In the CONTROL-1, DC, CONTROL-2, and NIF-DC groups, there were no significant differences in the 87-lead ECG parameters in patients with or without recurrence of ventricular tachyarrhythmias.

3.5. Inter- and intra-observer variabilities

There were no significant differences inter- and intra-observer variabilities.

4. Discussion

The major finding of the present study is that administration of NIF significantly suppressed the deterioration of SDR just after ICD shock. To the best of our knowledge, this is the first study to show that NIF significantly reduces the SDR after ICD shock in patients receiving oral amiodarone and β-blocker agents. A recent study reported that the SDR after ICD shock played an important role in the initiation and maintenance of ventricular tachyarrhythmias [5–7]. We therefore speculate that the reduction in SDR may be one of the mechanisms by which NIF suppresses the recurrence of ventricular tachyarrhythmias just after ICD shock in the presence of oral amiodarone and β-blocker administration.

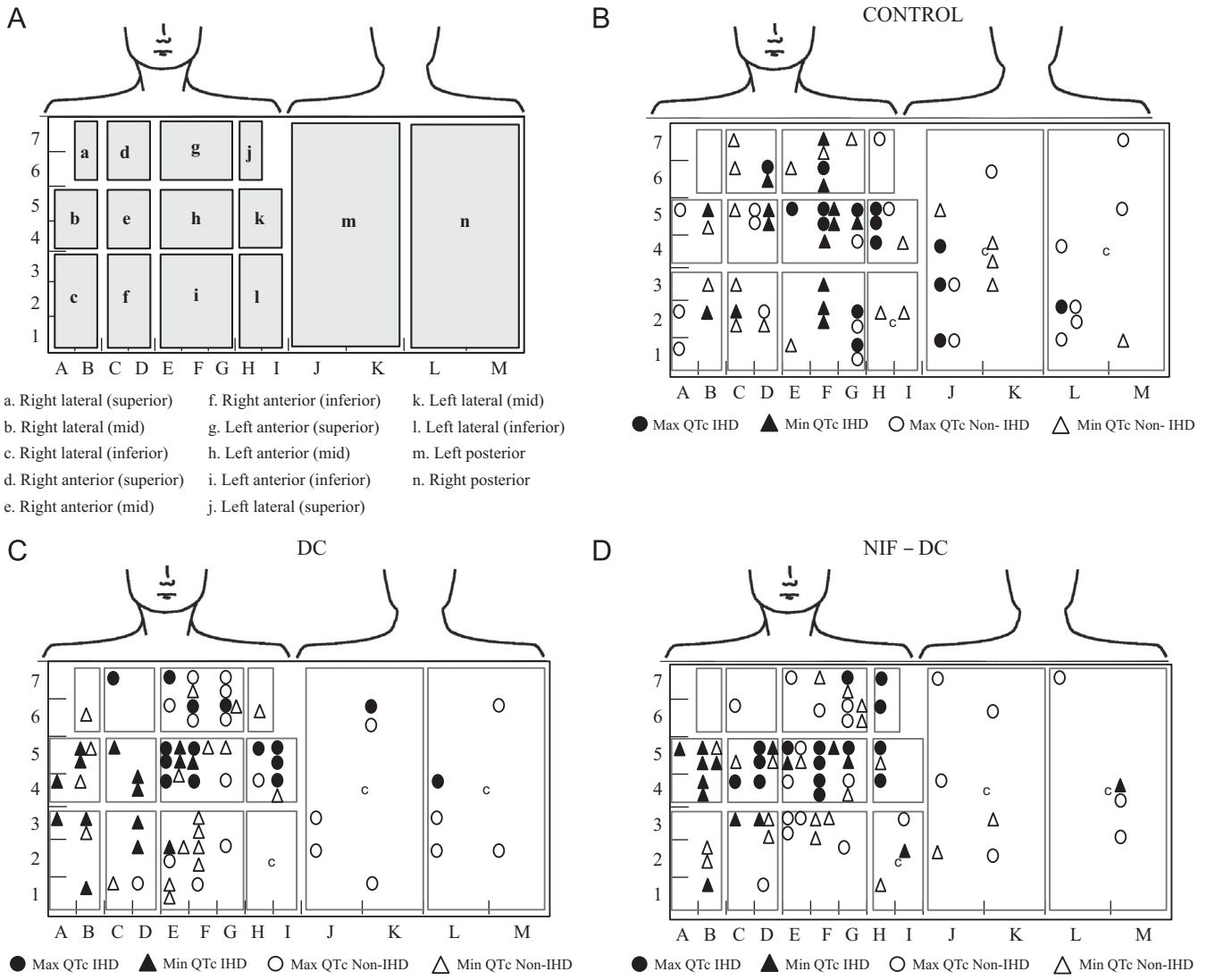

Fig. 5. The location of the max QTc and min QTc among the CONTROL, DC, and NIF-DC groups were plotted, and compared between ischemic heart disease (IHD) and nonischemic heart disease (non-IHD) patients. Columns A and B correspond to the right lateral region. Columns C and D correspond to the right anterior region. Columns E, F, and G correspond to the left anterior region. Columns H and I correspond to the left lateral region. Columns J and K correspond to the left posterior region, whereas columns L and M correspond to the right posterior region. We divided the 7 rows into inferior, middle, and superior side (rows 1–3, 4, and 5–7, respectively).

4.1. Effects of NIF on SDR

Some studies have reported that electrical shock produces different degrees of action potential duration and dispersion of repolarization [5,6]. In the present study, ICD shock increased the QTc-D, as has been reported previously [5,6]; however, the deterioration of QTc-D did not continue for 30 min because there were no differences in any parameter between the CONTROL-1 and CONTROL-2 groups. NIF is known to block the delayed rectifier K^+ channel, especially the I_{kr} channel [9,10], which results in a prolonged action potential duration. The blocking effect of NIF on the I_{kr} channel has been reported to occur rapidly, but recovery from the block is slow [9]. On the other hand, amiodarone has many effects including blockade of β-adrenergic receptors, the first inward Na^+ current, the L-type Ca^{2+} current, and the fast and slow components of delayed rectifier potassium current (I_{kr} and I_{ks}); especially, long-term treatment of amiodarone reduces I_{ks}. Several clinical studies have demonstrated that amiodarone prolongs the QTc interval and reduces or does not change the QT dispersion [14–16]. In this study, all patients were taking oral amiodarone and β-blocker agents. NIF has a reverse use-dependent blocking action [17]. In addition, an I_{kr} channel blocker can enhance QT prolongation especially during bradycardia and may cause torsade de pointes owing to an increase in transmural dispersion of repolarization [18,19]. The use of NIF and β-blocker may increase the SDR, but the combination of oral amiodarone and β-blocker may have relatively little effect on the SDR. Depending on these basic pharmacological effects, in the clinical setting, most of the patients with electrical storm and impaired left ventricular function due to structural heart diseases take oral amiodarone and β-blocker agents. In our study, NIF prolonged the max and min QTc after ICD shock. In particular, we found significant prolongation of the min QTc in the NIF-DC group compared with the DC group. On the other hand, we found that the location of the max and min QTc became closer in the NIF-DC group compared with the DC group, which is believed to be a situation that could easily lead to the progression of reentrant ventricular tachyarrhythmias. We therefore suggest that the prolongation of the min QTc after NIF administration may play an important role in reducing the QTc-D in the whole heart, ever after ICD shock, and that the effect of NIF may occur before the undesirable situation that progresses reentrant ventricular tachyarrhythmias, and result in the prevention of subsequent ventricular tachyarrhythmias after ICD shock to some degree, even with oral amiodarone and β-blocker administration.

The previous experimental studies under long QT conditions have suggested the possibility of ventricular tachyarrhythmia, especially torsade de pointes, occurring under conditions of NIF administration [18,19]. In this study, neither ventricular tachyarrhythmia nor torsade de pointes was observed after NIF administration despite QTc prolongation. We confirmed that the loading dose of NIF ($0.3\ mg\ kg^{-1} \cdot 10\ min^{-1}$) is safe even for administration immediately before ICD shock.

Fig. 5 shows that the area of max QTc and min QTc in patients with non-IHD was located more widely than that in patients with IHD. One of the reasons for this finding is that in patients with non-IHD, the myocardial damage is distributed diffusely, whereas it has been found to be distributed focally in patients with IHD. We found no differences in any parameters between IHD and non-IHD patients, which might be attributable to the small number of patients examined and/or those taking amiodarone and β-blocker agents.

4.2. Feasibility of using NIF for the treatment of electrical storms

NIF, a pure K channel blocker, does not have negative inotropic effects and does not affect cardiac conduction. In addition, it can only be used intravenously and its half-life is relatively short. Moreover, NIF has also been reported to decrease the defibrillation threshold [20]. Although close monitoring of the QT interval is needed, NIF may be suitable for the suppression of early recurrence of ventricular tachyarrhythmias just after ICD shock.

4.3. Study limitations

This study has several limitations. First, all patients were receiving oral amiodarone. Several clinical studies have demonstrated that amiodarone prolongs the QTc interval and reduces or does not change the QT dispersion [14–16]. In this study, the QTc in the CONTROL-1 and CONTROL-2 groups was slightly prolonged. Oral amiodarone could have modified the change in ECG parameters in the DC and NIF-DC groups. In the clinical setting, however, most patients with reduced left ventricular function and frequent episodes of drug-intolerable ventricular tachyarrhythmias receive oral amiodarone and/or a β-blocker. Although we could not show an NIF effect under conditions without oral antiarrhythmic drugs, our findings may be applicable to the clinical setting. Second, we did not find a positive correlation between the dispersion of repolarization and the recurrence of ventricular tachyarrhythmias. It may be difficult to predict the recurrence of ventricular tachyarrhythmias including electrical storms, by using the ECG parameters of repolarization before and after ICD shock. It may be premature to draw conclusions with the small number of patients examined, and this may be an important issue for future research.

5. Conclusion

NIF suppressed the deterioration of SDR just after ICD shock. This might be one of the mechanisms by which NIF suppresses the recurrence of ventricular arrhythmias just after ICD shock in the presence of amiodarone and β-blocker treatment.

Disclosure

The authors did not receive any financial support.

Conflicts of interest

None.

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