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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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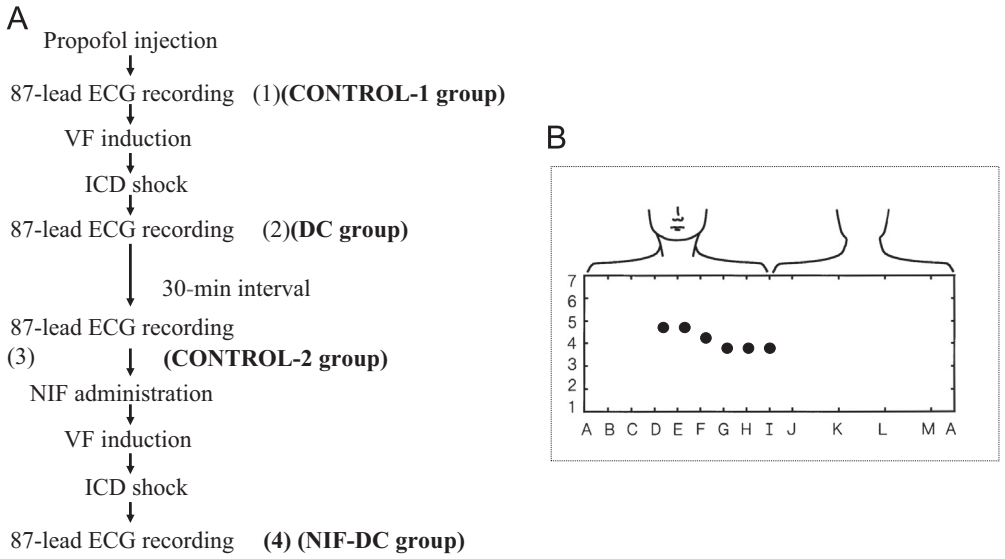

Fig. 1. (A) Protocol of this study. The 87-lead body surface ECG was recorded 4 times in all patients [(1)–(4)]: (1) CONTROL-1 group, during sinus rhythm after injection of propofol; (2) DC group, just after termination of induced VF by ICD shock; (3) CONTROL-2 group, 30 min after ICD shock, before administration 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).