Can Nifekalant Hydrochloride be Used as a First-Line Drug for Cardiopulmonary Arrest (CPA)?

— Comparative Study of Out-of-Hospital CPA With Acidosis and In-Hospital CPA Without Acidosis —

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Background Early defibrillation of ventricular tachycardia and fibrillation (VT/VF) is an urgent and most important method of resuscitation for survival in cardiopulmonary arrest (CPA). We have previously reported that nifekalant (NIF), a specific I_{Kr} blocker developed in Japan, is effective for lidocaine (LID) resistant VT/VF in out-of-hospital CPA (OHCPA). However, little is known about the differences in the effect of NIF on OHCPA with acidosis and in-hospital CPA (IHCPA) without acidosis.

Methods and Results The present study enrolled 91 cases of DC shock resistant VT/VF among 892 cases of CPA that occurred between June 2000 and May 2003. NIF was used (0.15–0.3 mg/kg) after LID according to the cardiopulmonary resuscitation (CPR) algorithm of Tokai University. The defibrillation rate was higher in the NIF group for both OHCPA and IHCPA than for LID alone, and the VT/VF rate reduction effect could be maintained even with acidosis. However, sinus bradycardia in OHCPA, and torsades de pointes in IHCPA were occasionally observed. These differences in adverse effects might be related to the amount of epinephrine, serum potassium levels, serum pH, and interaction with LID.

Conclusions NIF had a favorable defibrillating effect in both CPA groups, and it shows promise of becoming a first-line drug for CPR. (Circ J 2006; 70: 21–27)

Key Words: Acidosis; Cardiopulmonary resuscitation; Nifekalant hydrochloride; QT prolongation; Ventricular fibrillation

It is well known that a substantial number of sudden cardiac deaths caused by out-of-hospital cardiopulmonary arrest (OHCPA) is related to ventricular tachycardia and ventricular fibrillation (VT/VF).^{1,2} Prehospital cardiac arrest in Japan occurs in approximately 30,000 persons each year because of acute coronary syndrome, and most die of fatal arrhythmias.³ The American Heart Association (AHA) Guideline 2000 for cardiopulmonary resuscitation (CPR)^{4,5} recommends intravenous amiodarone to prevent recurrent VT/VF^{6,7} but that drug has not yet been approved in Japan.

There was not an effective agent for VT/VF refractory to class I drugs until nifekalant hydrochloride (NIF) was developed in Japan and it is the only first class III intravenous agent approved by Japanese medical and health insurance. It is expected that NIF will have a defibrillating effect on refractory VT/VF because intravenous NIF interferes with the delayed rectifier K^+ channels, particularly the

rapid component of the current I_{Kr} , as well as the inward-rectifier K^+ current I_{K1} and transient outward K^+ channel I_{to} .^{8–11} resulting in significantly prolonging of the duration of the action potential, which has a potent antiarrhythmic effect.¹² In addition, when combined with the use of direct-current cardioversion (DC) shock it will facilitate defibrillation, because NIF reduces the defibrillation threshold.¹³ NIF is also useful for ischemia-induced VT/VF because it inhibits the adenosine triphosphate (ATP)-sensitive potassium channels under ischemic and hypoxic conditions.^{14–16} The only disadvantage of NIF is very prolonged QT intervals, especially with bradycardia under the conditions of reverse use dependent block⁸ and there is a risk of torsades de pointes (Tdp).¹⁷

There have been many reports of the efficacy of NIF for ischemic heart disease (IHD) after the Dor operation^{18–19} and in patients undergoing hemodialysis.²⁰ NIF is also effective for ventricular arrhythmia when there is severe ventricular dysfunction.²¹ It is clear that NIF would be a suitable agent for CPR, but no universal standardized guidelines for its use have been prepared, because there has been little evidence of its efficacy in cardiopulmonary arrest (CPA) patients. We first started to use NIF according to our original CPR protocol²² as an alternative for amiodarone, and we found that it was more effective in the OHCPA patients. However, 1 patient experienced sudden sinus arrest after successful defibrillation with NIF and one of the reasons

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Fig 1. Cardiopulmonary resuscitation algorithm for the treatment of ventricular fibrillation (VF)/pulseless ventricular tachycardia (VT) developed at Tokai University. Primary ABCD and first direct-current cardioversion (DC) shocks were administered for VT/VF. In secondary ABCD for recurrent VT/VF, epinephrine infusion and further DC shocks were given. A single dose of lidocaine (LID) was first injected in combination with DC shock, and then the subjects were divided into 2 groups that were treated by different protocols: the non-nifekalant (NIF) and the NIF groups. Additional LID was injected again up to a maximum dose of 3 mg/kg in combination with DC shocks, and magnesium sulfate or procainamide were administered if required with further DC shocks. NIF was injected slowly over 5 min in combination with the DC shocks, additional NIF administration with further DC shocks were used for persistent or recurrent VT/VF.

for the sinus arrest was the acidotic condition of the patient. We therefore prospectively investigated the differences in the effect of NIF in OHCPA cases with acidosis and in-hospital cases (IHCPA) without acidosis, and evaluated the positive benefits against the risks of NIF to determine whether NIF can be used as a first-line drug for both OHCPA and IHCPA.

Methods

Subjects

A total number of 892 CPA patients in Tokai University were enrolled between June 2000 and May 2003 (780 OHCPA patients transported by ambulance, 112 IHCPA patients). VF incidence in the general population was 32.5% (237 OHCPA and 53 IHCPA patients), in which the incidence of first DC-shock-resistant VF was 31.4% (46 OHCPA, 47 IHCPA patients). The resuscitation protocol of this study was applied in 65 CPA patients (36 OHCPA, 29 IHCPA patients) who had a primary cardiac arrest witnessed by bystanders. Of the 36 OHCPA cases, CPR was performed by bystanders in 8 patients (22.2%). VT/VF was detected by the staff of the emergency medical service (EMS), and primary DC shock was given to 10 patients (27.8%). The low percentage of DC application was because the EMS were not authorized to apply DC shock without comprehensive instructions by a doctor until the April 2003 Revision of Law Concerning Emergency Life Guards in Japan. Primary CPR with DC shock was performed by a doctor for all the IHCPA patients.

According to the protocol, the 65 DC-shock-resistant VT/VF patients were divided into 2 groups after initial lidocaine (LID) injection: (1) additional LID plus magnesium sulfate and procainamide if necessary (non-NIF group), and (2) additional NIF (NIF group). The patients who were successfully defibrillated by the first dose of LID were also included in the non-NIF group for analysis ($n=11$). In the non-NIF-group there were 44 patients (32 males, 12 females; mean age 67 ± 8.1 years). The underlying disease was acute myocardial infarction (AMI: 7 patients), IHD (7 patients), old myocardial infarction (OMI: 13 patients), hypertrophic cardiomyopathy (HCM: 1 patient),

dilated cardiomyopathy (1 patient), Brugada syndrome (1 patient), and hypertension (HT: 14 patients). In the NIF-group there were 21 patients (15 males, 6 females; mean age 63 ± 9.2 years) and the underlying diseases were AMI (8 patients), IHD (4 patients), OMI (4 patients), HCM (2 patients), idiopathic VT (1 patient), and HT (2 patients). All patients were classified into 4 groups based on the location of CPA onset and the type of medication administered for CPR: Group A (OHCPA, non-NIF group; $n=24$), Group B (IHCPA, non-NIF group; $n=20$), Group C (OHCPA, NIF group; $n=12$), and Group D (IHCPA, NIF group; $n=9$).

Methods

CPR was performed according to the algorithm for treatment of VF and pulseless VT developed at Tokai University based on the 2000 AHA guidelines (Fig 1). Primary CPR was performed with DC shocks (200 J, 300 J, and 360 J). Persistent or recurrent VT/VF was treated by secondary CPR and epinephrine infusion (1 mg every 3–5 min), and further DC shocks (360 J). A single dose of LID (1.0 mg/kg) was injected concomitantly with the DC shocks (360 J up to 3 times). The patients were then divided into 2 groups treated by 2 different protocols (non-NIF and NIF groups). In the non-NIF group, additional LID (1.0 mg/kg) was injected up to a maximum dose of 3 mg/kg in combination with the DC shock (360 J up to 3 times), followed by intravenous (IV) injection of magnesium sulfate (1–2 g/min) or procainamide (30 mg/min) and further DC shocks (360 J). In the NIF group, NIF (0.15 mg/kg) was injected slowly IV over 5 min, and after the injection, DC shocks were administered at increasing energy levels from 200 J to 360 J. Additional NIF (0.15 mg·kg⁻¹·5 min⁻¹) and further DC shocks (360 J up to 3 times) were administered for persistent or recurrent VT/VF. Although cardiac massage was continued during the NIF administration, epinephrine injection was avoided because of potential interactions with NIF. Continuous limb-lead electrocardiographic monitoring was used to detect the decrease in ventricular rate caused by the bradycardic effect of the treatment. NIF dip intravenous (Div) infusion after defibrillation was administered only for the patients in whom there was ventricular premature contractions (VPCs) or non-sustained VT; the starting

Fig 2. Defibrillation rate in the non-nifekalant (NIF) and NIF groups. (Left) Schema of the result of defibrillation. Direct-current cardioversion (DC) shock applications following lidocaine (LID) caused sinus rhythm in 11 patients but failed in 54 patients. Additional administration of LID was given to 33 patients and NIF was given to 21 patients. As a result, successful defibrillation was 19/44 in the non-NIF group, and 17/21 in the non-NIF group. (Right) Comparison of the defibrillation effect in the non-NIF and NIF groups. Successful defibrillation rate in response to LID was lower in the out-of-hospital cardiopulmonary arrest (OHCPA) cases (Group A) than in the in-hospital cardiopulmonary arrest (IHCPA) cases (Group B), (17% vs 75%). Successful defibrillation rate in the response to NIF was greater in both OHCPA (Group C) and IHCPA cases (Group D) (75% vs 89%).

Fig 3. Correlation between defibrillation success rate and the presence of acidosis in the non-nifekalant (NIF) and NIF groups. Abscissas: the interval between cardiopulmonary arrest (CPA) onset and initiation of cardiopulmonary resuscitation (CPR) by a doctor. Data were obtained from both the non-NIF group (Left) and the NIF group (Right). Ordinates: serum pH. Defibrillation success in the non-NIF group is represented by the white diamonds (◇), $R=0.742$, $R^2=0.550$, $p=0.0003$, and that in the NIF group is represented by the white circles (○), $R=0.742$, $R^2=0.551$, $p=0.0006$. Defibrillation failures in the 2 groups are represented by the black diamonds (◆) and circles (●). IHCPA, in-hospital CPA; OHCPA, out-of-hospital CPA.

dose was set at 0.15 mg/kg and increased to $0.4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ with QTc interval monitoring. The first dose of LID and NIF were set at less than the usual doses for these drugs in our protocol, because of concerns about possible side effects on account of the unstable hemodynamics and severe heart dysfunction associated with CPA.

The NIF protocol was used when the patients were seen on days that were multiples of 3 in order to avoid misunderstanding of the protocol, because instructions to administer it on even or odd days caused confusion. The non-NIF protocol was selected when the patient was seen on the other days. Immediately after CPA was confirmed, blood specimens were drawn from the femoral artery to determine the plasma potassium level (mmol/L) and blood pH. Percutaneous cardiopulmonary support (PCPS), temporary pacemaker and other drugs (potassium chloride and sodium bicarbonate) were used as required. All the emergency care unit teams were equally skilled at CPR. The research was conducted after obtaining the approval of the Ethical Review Board. Appropriate consideration was given to ethical and safety aspects during the study; however, we were prohibited from conducting a double-blind study using NIF alone because the currently available first-line drugs for pharmacological defibrillation in Japan are LID and pro-

cainamide, and NIF is only permitted for use as a second-line drug for VT/VF.

Statistical Analysis

All measurements are presented as means $\pm$ SD (standard deviation). The t-test and χ^2 test were used to test differences in means between the 2 groups for statistical significance, with $p < 0.05$ considered indicative of statistical significance. Correlation coefficients were also examined for defibrillation conducted under the condition of acidosis.

Results

Defibrillation Efficacy in the Non-NIF and NIF Groups (Fig 2)

Sinus rhythm was restored in 43% (19/44) of the non-NIF group and 81% (17/21) of the NIF group. A PCPS was used for 1 HCM patient only in the non-NIF group, and temporary pacemakers were used for 2 sinus arrest patients in the NIF group after sinus rhythm was restored.

The successful defibrillation rate of OHCPA was significantly lower than that of IHCPA ($p < 0.05$) in the non-NIF group. Defibrillation failed in 25 patients, who eventually died from asystole ($n=20$), persistent VT/VF ($n=3$), or

Fig 4. Bradycardic effect of nifekalant (NIF) administered in combination with direct-current cardioversion (DC) shocks. Abscissas: ventricular tachycardia (VT)/ventricular fibrillation (VF) rate (beats/min). Data were obtained from the 12 out-of-hospital cardiopulmonary arrest (OHCPA) (Left) and 9 in-hospital cardiopulmonary arrest (IHCPA) (Right) cases in the NIF group. Defibrillation success is represented by the open circles (○) and triangles (△), whereas defibrillation failure is represented by the filled circles (●) and triangles (▲). The mean VT/VF rate decreased by 29.6% in the OHCPA cases and by 26.2% in the IHCPA cases after NIF infusion. Sinus rhythm was restored in 17/21 patients in total who received NIF in combination with DC shocks.

recurrent VT/VF ($n=2$). Whereas, in the NIF group, the successful defibrillation rate was more than 75% in both OHCPA and IHCPA. Four patients failed defibrillation and eventually died from asystole ($n=1$), persistent VT/VF ($n=1$) or recurrent VF ($n=2$).

Correlation Between Defibrillation Success and Acidosis in the Non-NIF and NIF Groups

Fig 3 shows the relationship between the success/failure of CPR and the time from the CPA (CPA interval) and the serum pH. The CPA interval was defined as the interval between the time a CPA was witnessed by a bystander and the initiation of CPR by a doctor. Data were obtained for both the non-NIF and NIF groups. There were significant correlations between successful defibrillation and the blood pH and CPA interval in both the non-NIF group ($R=0.742$, $R^2=0.550$, $p=0.0003$) and NIF group ($R=0.742$, $R^2=0.551$, $p=0.0006$). However, although the correlation between defibrillation failure and these parameters was not significant in the non-NIF group ($R=0.264$, $R^2=0.070$, $p=0.2608$), the number of cases of failed defibrillation in the NIF group was too small to allow reliable analysis. Defibrillation success in severe acidotic cases was obtained more often in the NIF group than in the non-NIF group.

Bradycardic Effect of NIF in Combination With DC Shocks

The ventricular rate before and after NIF infusion was monitored to examine the bradycardic effect of the treatment (Fig 4). Data were obtained from 12 OHCPA cases and 9 IHCPA cases in the NIF group. The mean VT/VF rate in the OHCPA cases was 185 ± 37.5 beats/min before

Table 1 Background of the Out-of-Hospital and In-Hospital Cases of CPA in the NIF Group

Characteristics	OHCPA	IHCPA	
<i>n</i>	12	9	NS
Age (years)	63 ± 10.0	66 ± 13.9	NS
Male	7 (58%)	8 (89%)	NS
Dose of epinephrine (mg)	18 ± 8.6	2 ± 2.2	$p < 0.05$
Dose of LID (mg)	104 ± 45.0	117 ± 50.0	NS
Dose of NIF (mg)	15 ± 3.1	15 ± 2.4	NS
Number of DC shocks	8 ± 7.3	5 ± 6.2	NS
Serum K^+ level (mmol/L)	4.5 ± 0.91	3.6 ± 0.35	$p < 0.05$
Serum pH	7.08 ± 0.205	7.35 ± 0.113	$p < 0.05$
ROSC (%)	9/12 (75%)	8/9 (89%)	NS
Admitted ICU (%)	8/12 (67%)	7/9 (78%)	NS
QTc interval (ms)	0.43 ± 0.064	0.60 ± 0.060	$p < 0.05$
Occurrence of Tdp (%)	0/8 (0%)	1/7 (14%)	NS
Sinus suppressive effect (%)	4/8 (50%)	0/7 (0%)	NS

Values are mean $\pm$ SD. Data were obtained during cardiopulmonary resuscitation and after successful defibrillation.

CPA, cardiopulmonary arrest; NIF, nifekalant; OHCPA, out-of-hospital CPA; IHCPA, in-hospital CPA; LID, lidocaine; DC, direct-current cardioversion; ROSC, return of spontaneous circulation; ICU, intensive care unit; Tdp, torsade de pointes.

Significant value < 0.05 .

NIF infusion, and it decreased by 29.6% after NIF infusion (130 ± 46.9 beats/min). In the IHCPA cases, the mean VT/VF rate was decreased by 26.2% (from 215 ± 39.2 beats/min to 159 ± 43 beats/min). NIF exerted a significant bradycardic effect in 17/21 patients in total; 2 of these patients were OHCPA cases and did not require DC cardioversion to obtain sinus rhythm because the VT converted to sinus rhythm with NIF infusion alone, and the remaining 15 patients needed DC shocks for cardioversion. DC shocks were required in cases of VT/VF with a rate of 150 beats/min or higher, and in almost all of these cases sinus rhythm was achieved with a single DC shock of 200 or 300 J. The defibrillation efficiency of NIF with DC shock was maintained even under the condition of acidosis.

Comparison of the Background of the OHCPA and IHCPA Cases in the NIF Group

The baseline characteristics, CPR implementation, and prognosis of the OHCPA and IHCPA cases in the NIF group are shown in Table 1. The doses of the drugs used are the total amount of the drug used during the CPR. There was no significant difference in the number of patients, mean age, sex, dose of LID (mg), dose of NIF (mg) or number of DC shock procedures. However, the serum potassium level (mmol/L) in the initial arterial blood specimen and the dose of epinephrine (mg) were significantly higher in the OHCPA cases, and pH was significantly lower in the OHCPA than IHCPA ($p < 0.05$, respectively). The different environmental factors between the OHCPA and IHCPA cases triggered 2 types of undesirable pharmacological effects. The QTc interval was markedly prolonged (0.60 ± 0.060 ms averaged) and Tdp occurred in 1 patient (14%) among the IHCPA cases. Sinus suppression (sinus brady cardia and sinus pause) was observed in 4 patients (50%) who were all OHCPA cases.

Return of spontaneous circulation was favorable in both OHCPA cases (75%) and IHCPA cases (89%). The rate of admission to the intensive care unit was 67% in the OHCPA group and 78% in the IHCPA group; thus, the primary endpoint was obtained at an excellent rate in both the IHCPA and OHCPA groups receiving NIF. However, the 1-month

survival and full recovery rates were 17% (2/12) and 0% (0/12), respectively, in the OHCPA cases, and were better at 44% (4/9) and 44% (4/9), respectively, in the IHCPA cases (data not shown in the Table). The OHCPA patients died not because of recurrence of VT/VF, but because of non-cardiac causes associated with post-resuscitation encephalopathy.

Discussion

The major findings of the present study are: (1) NIF was very useful for the treatment of VT/VF in both OHCPA and IHCPA compared with the non-NIF group, (2) defibrillation and bradycardiac effects of NIF were maintained even in acidosis, and (3) occasionally sinus node suppression occurred in the OHCPA cases, and excessive QT prolongation and Tdp occurred in the IHCPA cases after defibrillation success by NIF.

Pharmacological Properties of LID in Acidosis

The most radical and major difference between the IHCPA and OHCPA cases was the long time taken to achieve defibrillation success in the OHCPA cases. It takes a long time from the onset of CPA to the initiation of CPR in OHCPA cases, which is associated with progression of metabolic acidosis in these cases. Acidosis may aggravate the loss of myocardial contractility and also reduce the success rate of defibrillation. The rate of successful defibrillation by NIF administration was high in the out-of-hospital cases, as opposed to the low defibrillation rate by LID. One of the reasons for the poor defibrillation effect of LID is that the drug's characteristics are modified in acidosis and it loses its normal kinetics.²³ When LID enters the cell through a sodium ion channel from the extracellular area, it mainly takes a non-polarized form at normal pH and traverses the hydrophobic pathway (fast kinetic drug). However, under the conditions of low pH LID is electrically charged and takes the polarized form because the number of protons increases in the extracellular area and thus LID cannot traverse the hydrophobic pathway. As a result, degradation of LID is delayed and the dependent-sodium channel suppressive effect is substantially enhanced (slow kinetic drug). The longer the time delay to CPR, the more negative inotropic actions are increased, and the well-known proarrhythmic properties of sodium-channel blockers may be involved.^{24–26} Acidosis would decrease the chances of defibrillation success by LID.

QT Prolongation is Effected by the Interaction Between Epinephrine and NIF

The QTc interval was significantly more prolonged after NIF infusion in the IHCPA than in the OHCPA cases, despite the administration of NIF at the same dose to both groups. Clinically, the blood concentration of NIF is usually reflected in the QTc interval on 12-lead ECG, and would be a predictive factor of Tdp. Conventionally, a QTc interval less than 0.5 ms is an indicator of the pharmacological effect, but it was not a dependable marker in the OHCPA patients, one of the reasons being the catecholamine effect in protracted myocardial ischemia.^{14–16} Because activation of KATP in the myocardium associated with the hypoxic condition affects the I_{Ks} , thus, combined use with a catecholamine relatively counteracts the effect of the I_{Kr} blocker. High-dose epinephrine may worsen this reaction, and the action potential duration (APD) prolongation effect

of NIF may be suppressed. The significantly less pronounced QT prolongation effect in the OHCPA cases may be attributable to these interactions. Therefore, epinephrine injection should be avoided during NIF administration.

Much caution must be exercised when intravenous catecholamines are administered concomitantly with NIF Div. It has been reported that combined use of I_{Kr} blockers (E403-1) and β receptor agonists indicated that these drugs were likely to alter the APD (phenomenon of shortening and prolongation), and thus instability in repolarization can lead to the onset of Tdp.²⁷ APD alteration may also occur during concomitant NIF and epinephrine administration, so it is important to note that any dose reduction or withdrawal of catecholamine has the potential to cause abrupt QT prolongation.

The serum potassium level also affects the activity of I_{Kr} blockers. For the same dose of NIF, the total potassium current is more strongly inhibited in the presence of hypokalemia than under the conditions of normo- or hyperkalemia. Because the serum potassium levels were higher in the OHCPA than in the IHCPA cases, the effect of NIF on decreasing the total potassium current may have been less pronounced in the OHCPA cases, resulting in an inadequate APD prolongation effect in these cases as compared with the IHCPA cases. Another explanation is that Tdp is more easily induced in the presence of low serum potassium concentrations. Thus, any electrolyte abnormalities detected must be corrected during the use of NIF.

Adverse Reactions of NIF on the Sinus Node With Concomitant Use of Epinephrine and LID

Sinus suppression was observed in 50% of patients in the OHCPA group only. The etiology of the sinus suppression remains unclear, but suggested causes include: (1) progression of metabolic acidosis associated with CPA leading to reduced effects of intrinsic catecholamines and resulting in a reduced β agonistic effect; (2) the absence of any atrial or ventricular escape rhythm, so ischemia has a diffuse suppressive effect on conduction involving the sinus node, atrioventricular node, and Purkinje fibers; (3) extrinsic catecholamines having a suppressive effect on the sinus node (ie, activation of I_{Ks} by NIF leading to relative suppression of I_{K1} of the sinus node); and (4) interaction between LID and NIF causing an increased suppressive effect on I_{Kr} , I_{Ks} and I_{Na} within the sinus node. The distribution of plural ion channels within the sinoatrial node suggests regional differences in drug effect; for example, the density of I_{Kr} is greater in the periphery of the sinus node.^{28,29} If the sinus node is severely affected (eg, ischemia, drug, ageing, etc), the pacemaker reserve function is activated to compensate for the lost ion current.³⁰

For these reasons, the combined use of LID and NIF may not be suitable, and it is necessary to use a minimal dose of epinephrine to trigger and maintain the reserve potential of the sinus node. In addition, the first dose of NIF should be administered at 50% ($0.15 \text{ mg} \cdot \text{kg}^{-1} \cdot 5 \text{ min}^{-1}$) of the normal dose ($0.3 \text{ mg} \cdot \text{kg}^{-1} \cdot 5 \text{ min}^{-1}$). In fact, damage to the sinus node is related mainly to progression of acidosis and ischemia, therefore a temporary pacemaker must be available for back-up pacing. However, if sinus function is almost maintained, as in the IHCPA cases, a single dose of LID before the administration of NIF is permitted. Because LID has a short half life in humans, additional doses of NIF may not be as affected by LID, but more than 10 min wash-out of LID is an absolutely requirement between NIF and

LID injections. Administration in the opposite order will interfere with each drug's pharmacological interaction because NIF has a long half life. If additional NIF is recommended, it should be given in divided doses as needed and NIF Div infusion after the defibrillation should be administered only for patients who have VPCs or non-sustained VT, because NIF has a longer wash-out period.

Combined use of NIF and LID may also have other unexpected disadvantageous effects besides sinus node suppression. In a preliminary study, Amino et al investigated the effects of combined NIF and LID administration on the functions of the left ventricle in rabbit hearts using an optical mapping system, and found that the pharmacological actions of NIF (0.5 μ mol/L) on the spiral excitations of the left ventricle were reversed by LID (3 μ mol/L).³¹ The APD prolongation caused by NIF was readily countered by the concomitant reduction of $I_{Na,slow}$ in response to LID; thus, the vulnerability to VF was significantly increased in the presence of both NIF and LID as compared with that in the presence of NIF alone. From also these reasons, LID administration after NIF or concurrent use of LID plus NIF is not recommended.

Adequacy of Either NIF or LID as a First-Line Drug for CPR

The successful defibrillation rate with NIF was superior to that of the non-NIF group in both OHCPA and IHCPA cases. However, the 1-month survival and full recovery rates were very poor in the OHCPA patients. The first reason for this finding would be the low frequency of bystander CPR and restricted administration of the primary DC shock by EMS staff; therefore, there was a more significant delay before NIF administration as secondary CPR in these cases as compared with that in the IHCPA cases. The chain-of-survival is the most important and promising approach for successful resuscitation, and the quick arrival of the paramedics' team and general education in lifesaving techniques are key factors in successful primary CPR.³² The second reason for the poor recovery would be the low defibrillation effect of LID in the OHCPA cases. The duration of circulatory arrest was reflected by the initial arterial blood pH in our study. These findings suggest that rapid defibrillation by a reliably effective agent is extremely important, and we recommend that NIF is the preferred first-line drug for CPR in cases with significant acidosis.

The present study has confirmed that NIF actually reduced the defibrillation threshold, as observed in canine experiments,¹³ whereas most sodium channel blockers increase the defibrillation threshold.³³ Dorian et al reported that LID administration for DC-shock-resistant VT/VF might need to be reviewed, because LID causes a concentration-dependent increase in defibrillation energy requirements. Weaver et al stated that LID was not be a suitable agent for CPR because of its negative inotropic action.³⁴ NIF does not have a negative inotropic action, and thus can be used in patients with decreased cardiac function.³⁵ On the other hand, the disadvantage of NIF is the rather complex method of emergency administration and the requirement for monitoring of the QT interval. It may be better to use LID in cases of IHCPA without acidosis than NIF to prevent undesirable effects, such as Tdp. We conclude that either NIF or LID may be an appropriate first-line drug for IHCPA cases, but NIF may be preferred for OHCPA cases.

Study Limitations

This study was not a double-blind study comparing LID alone with NIF alone, because the use of NIF alone is not yet officially approved for use as a first-line drug; LID had to be administered first to all cases as per the protocol, and NIF was often used in combination with LID.

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