ORIGINAL ARTICLE

Is the combination therapy of IKr-channel blocker and left stellate ganglion block effective for intractable ventricular arrhythmia in a cardiopulmonary arrest patient?

Mari Amino[1], Koichiro Yoshioka[1], Seiji Morita[2], Hiroyuki Otsuka[2], Takeshi Yamagiwa[2], Kazuo Umezawa[2], Yoshihide Nakagawa[2], Isotoshi Yamamoto[2], Tadashi Hashida[1], Yuji Ikari[1], Sadaki Inokuchi[2], Itsuo Kodama[3] and Teruhisa Tanabe[1]

[1]Department of Cardiology, Tokai University School of Medicine, Isehara, Japan
[2]Department of Critical Care and Emergency Medicine, Tokai University School of Medicine, Isehara, Japan
[3]Research Institute of Environmental Medicine, Nagoya University, Frocho, Nagoya, Japan

Abstract

Background: *We have previously reported that the defibrillation success rate of intravenous nifekalant hydrochloride (NIF), a pure IKr-channel (IKr: the rapid components of the delayed rectifier potassium current) blocker, was more than 75% for lidocaine--resistant ventricular tachycardia and fibrillation (VT/VF) in patients with out-of-hospital cardiopulmonary arrest (CPA). However, there was no effective treatment for the remaining 25% of patients in whom defibrillation was unsuccessful. We hypothesised that the combination therapy of NIF and left stellate ganglion block (LSGB) was useful for defibrillation in NIF-resistant VT/VF and investigated its efficacy in a retrospective study.*

Methods and results: *We investigated sequentially 272 out-of-hospital CPA patients treated at Tokai University between April and December 2006. VT/VF occurred in 55 patients on arrival or during cardiopulmonary resuscitation (CPR). On the basis of our CPR algorithm, NIF was administered (0.15–0.3 mg/kg, i.v.) after the first direct-current cardioversion. NIF-resistant VT/VFs were observed in 15 out of 55 patients and LSGB was performed on 11 of these with administration of NIF. Sinus rhythm was restored in 7 patients following LSGB (64%) and complete recovery was achieved in 2 patients. In the non-LSGB group, however, all the patients died.*

Conclusions: *The combination therapy of intravenous NIF and LSGB was useful for defibrillation in intractable VT/VF. It is a potential and innovative treatment strategy for IKr-channel blocker resistant VT/VF.* (Cardiol J 2007; 14: 355–365)

Key words: combined therapy, nifekalant hydrochloride, left stellate ganglion block, out-of-hospital cardiopulmonary arrest, ventricular tachycardia, ventricular fibrillation

Address for correspondence: Mari Amino, MD, PhD
Department of Cardiology
Tokai University School of Medicine
143 Shimokasuya, Isehara 259–1193, Japan
Tel: +81 463 93 1121, fax: +81 463 93 6679
e-mail: mariam@is.icc.u-tokai.ac.jp

Introduction

Intravenous nifekalant hydrochloride (NIF), a pure IKr-channel blocker (IKr: the rapid components of the delayed rectifier potassium current), has been developed in Japan and has been used to treat patients with intractable ventricular tachycardia and fibrillation (VT/VF) instead of intravenous amiodarone (AMD), since the use of the latter has not been permitted in Japan. There are several clinical reports describing the effectiveness of NIF since its release in 1999 [1, 2]. It has been known to prolong significantly the refractory period [3] and decrease the defibrillation threshold [4]. A recent experiment using rabbit hearts has revealed one of the mechanisms involved in the early termination of spiral-type re-entrant VT by NIF [5]. The role of NIF as a first-line drug for patients of acute coronary syndrome (ACS) [1], electrical storm (ES) [6] and out-of-hospital cardiopulmonary arrest (CPA) [3, 7] has been established. However, no effective treatment for NIF-resistant intractable VT/VF has been available. We have reported that the defibrillation success rate of NIF was superior (> 75%) for intravenous lidocaine-resistant VT/VF in patients with out-of-hospital CPA. However, in the remaining 25% of cases it was unsuccessful. This situation must be addressed with urgency in order to establish another effective therapy for the management of intractable VT/VF.

It has been known that dispersion in refractoriness between the ischemic border zone and the normal zone is increased by left stellate ganglion (LSG) stimulation in an ischemic dog model, and this may enhance the opportunity for VF to occur [8]. In contrast, from the 1970s there have been many experimental and clinical reports concerning the anti-arrhythmic effect of blockade of the LSG (LSGB) for re-entrant fatal tachycardia [9, 10]. It has been reported that in humans sympathetic blockades are superior to conventional anti-arrhythmic therapy recommended by the advanced life support guidelines for the treatment of ES in recent myocardial infarction (MI) [11]. Although there are two methods for achieving sympathetic blockade, namely LSGB and the administration of an intravenous beta-blocker, LSGB was thought to be more suitable and safer than a beta-blocker for cardiopulmonary resuscitation (CPR), because the hemodynamic changes after LSGB were considered to be small, even during congestive heart failure [12]. We therefore hypothesised that a sympathetic blockade would combine the therapeutic effects of a pure IKr blocker and reinforce the defibrillation effect achieved by a single application of NIF. The aim of this study is to investigate the efficacy of the combination therapy of NIF and LSGB for patients with sustained VT/VF in out-of-hospital CPA.

Methods

Subjects and methods (Fig. 1)

A total of 272 out-of-hospital CPA patients were admitted to Tokai University Hospital between April and December 2006. Fifty-five patients manifested VT/VF on arrival or during CPR, while 217 patients manifested asystole or pulseless electrical activity (PEA). Electrical defibrillation was successful in 6 patients by using biphasic direct-current (DC) cardioversion alone, and 34 cases of shock-resistant VT/VF were restored by using NIF with DC cardioversion. The remaining 15 patients manifested NIF-resistant VT/VF, which was either recurrent or intractable. Of these 15 patients 11 underwent LSGB accompanied by additional NIF administration, while 4 patients did not undergo LSGB at the discretion of the attending physician because of the internal hemorrhagic risk of puncture and the cervical anatomical anomaly. One patient showed a decrease in platelets, 2 patients were taking anticoagulants and 1 patient had extensive old scarring of the skin structure around the neck caused by a past history of the facial burn.

The research was conducted after obtaining the approval of the Ethical Review Board. Sufficient consideration was given to the ethical and safety aspects during the study. CPR was performed according to the algorithm developed in Tokai University (Fig. 1) on the basis of the 2005 American Heart Association guidelines. Asystole and PEA were treated with epinephrine and atropine infusion (1 mg given every 3–5 min) and cardiac massage for 3 min, while VF and pulseless VT were treated with primary DC cardioversion (biphasic; 150 J). Persistent or recurrent VT or VF were treated by infusion of NIF (0.15 mg/kg) and sequential cardiac massage for 3 min before a pulse check. Further DC cardioversion (150 J) was performed on patients with sustained VT/VF. In the case of intractable VT/VF additional NIF was administered. While NIF was being administered, the injection of epinephrine was stopped in order to inhibit an increase in the IKs current (IKs: the slow components of the delayed rectifier potassium current). If successful defibrillation was achieved, continuous intravenous NIF was infused as a preventive measure against the recurrence of VT/VF. However, in patients with QT prolongation it was not permissible for NIF to be
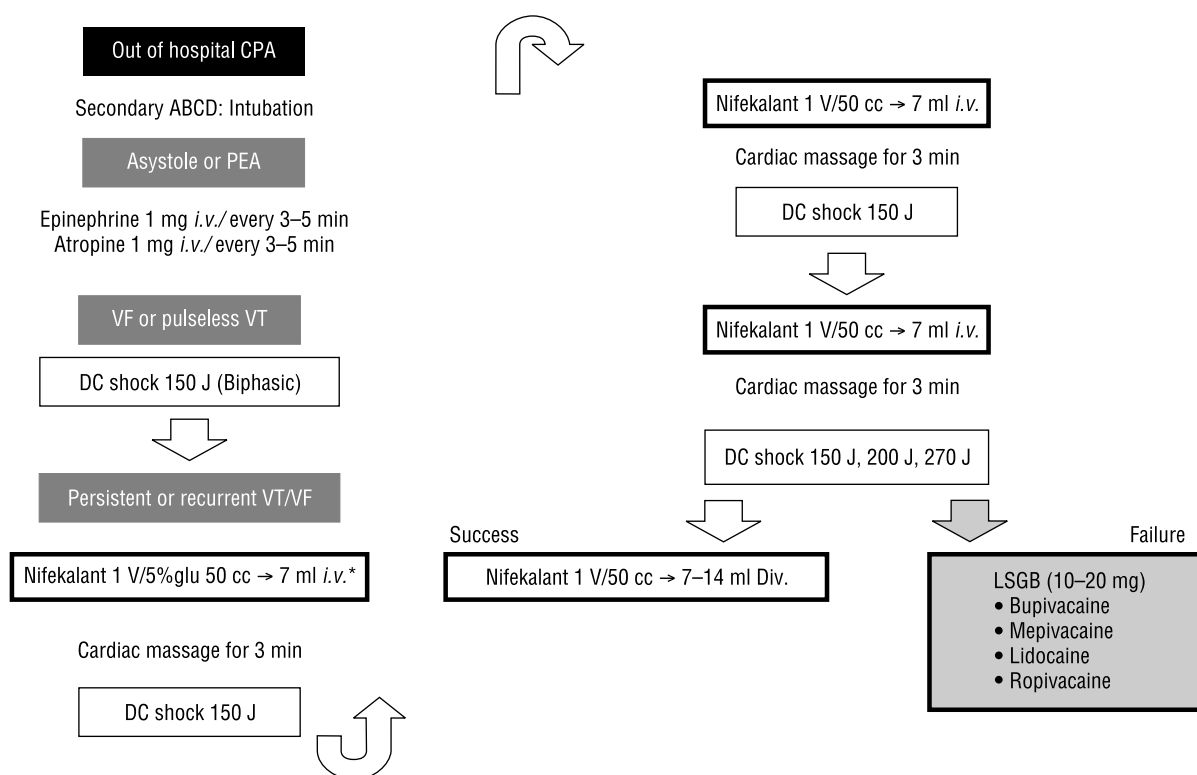
Figure 1. Algorithm of cardiopulmonary resuscitation (CPR) for patients with out-of hospital cardiopulmonary arrest (CPA) in Tokai University. Asystole and pulseless electrical activity (PEA) were treated with epinephrine and atropine infusion (1 mg given over every 3–5 min) and cardiac massage for 3 min, whereas pulseless ventricular tachycardia (VT) and fibrillation (VF) were treated with primary direct-current (DC) cardioversion (Biphasic, 150 J). Persistent or recurrent VT or VF was treated by infusion of nifekalant hydrochloride (0.15 mg/kg) and sequential cardiac massage for 3 min before a pulse check. Further DC cardioversion (150 J) was performed for patients with sustained VT/VF. In the case of intractable VT/VF, additional nifekalant hydrochloride was administered up to 3 times. If successful defibrillation was achieved, continuous intravenous nifekalant hydrochloride was infused as a preventive measure against the recurrence of VT/VF. However if not, left stellate ganglion block (LSGB) or after treatment was performed; *body weight 50 kg assumption; nifekalant hydrochloride 0.15 mg/kg conversion.

used as a first-line drug, and therefore lidocaine (LID) was the selected alternative.

Routine algorithms have not, on the other hand, been developed for NIF-resistant VT/VF. A percutaneous cardiopulmonary support system (PCPS), anti-tachycardia pacing by a temporary pacemaker, anti-arrhythmic drugs and other agents, including potassium chloride and sodium bicarbonate, were administered at the discretion of the attending physician. In the LSGB cases the local anesthetic agents, such as 0.5% LID, 0.25% bupivacaine, 1% mepivacaine, or ropivacaine (75 mg), were selected by the physician. The local anesthetic agent was injected in a stepwise manner (5 cc + 5 cc) with a 10 cc disposable syringe (23 G) into the basal part of the left transverse process of the sixth cervical spine (C6), taking care not to injure the left carotid artery. LSGB is conventionally used in the disease of the anesthesia department, and it is carried out for the pain control of the headache or the peripheral facial paralysis. It is one of the daily manual skills for the anesthesiologist, and thus the technique of LSGB is comparatively simple and easy for the critical care physician also.

As soon as CPR was initiated, blood specimens were drawn from the femoral artery to determine and correct the plasma potassium level (mEq/L), the blood pH and the lactate levels.

Statistical analysis

All measurements were presented as means ± ± SD. For evaluating the statistical significance the χ^2 test was used to test the differences between the mean values obtained for the defibrillation success and failure groups. $P < 0.05$ was considered to be statistically significant.
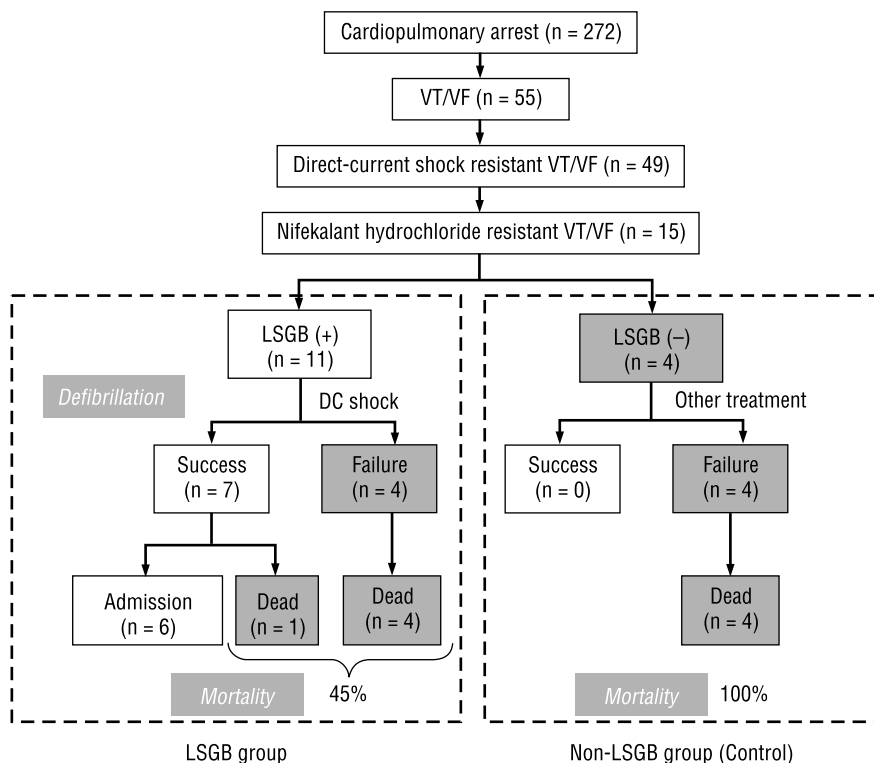
Figure 2. Defibrillation rate and mortality in the left stellate ganglion block group (LSGB group) and the non-LSGB group. Direct-current (DC) cardioversion applications following LSGB lead to sinus rhythm in 7 patients but failed in 4 patients. One of the success cases died from the recurrence of ventricular fibrillation (VF), while 4 patients in the LSGB group died from pulseless electrical activity. In the non-LSGB group, all patients died from VF. Mortality rate in response to LSGB was significant lower than in the non-LSGB cases (45% *vs.* 100%); VT — ventricular tachycardia.

Results

Defibrillation effect and mortality in the LSGB group *vs.* the non-LSGB group (Fig. 2)

LSGB was performed in 11 patients (the LSGB group), while in 4 patients it was not performed (the non-LSGB group) (Fig. 2). In the LSGB group sinus rhythm was restored after the performance of LSGB with the administration of NIF in 7 patients (the "successful" cases), but was not restored in 4 patients (the "failed" cases). DC cardioversion was required for all cases after LSGB, because sinus rhythm was not restored spontaneously by LSGB alone. Six of the successful cases were admitted into hospital, but 1 patient died from recurrent VF, while defibrillation combined with LSBG was unsuccessful in 4 patients, who eventually died, 1 from VF and 3 from asystole. In the non-LSGB group, in contrast, PCPS was used for 2 patients and procainamide was injected into another 2 patients, but they did not respond to treatment and died from VT/VF. Mortality after CPR was 45% in the LSGB group and 100% in the non-LSGB group.

Comparison of the characteristics of the successful and failed cases in the LSGB group (Table 1)

The 11 patients in the LSGB group were divided into two subgroups, namely the defibrillation success cases and the defibrillation failure cases, to determine the differences in CPR background. The ejection fraction of the heart, which was evaluated using echocardiography, was considered as the reference, because echocardiography was performed in different situations in different individuals (the data of the 7 successful patients were obtained after CPR, while for 4 patients the data obtained before CPA was substituted). The doses of drug administration were indicated as the total amount required during CPR. There were no significant differences between the defibrillation success and failure cases with respect to age, gender, ejection fraction, doses of epinephrine, LID, NIF, and LSGB or in the frequency of DC cardioversion. Furthermore, the serum K^+ levels the arterial blood pH and the serum lactate did not differ between the two groups. However, in the defibrillation failure groups, we observed a tendency toward hyperkalemia and acidosis. Short-term

Table 1. Comparison of the characteristics of the "success" and "failure" cases in the group of LSGB.

Characteristics	Success (n = 7)	Failure (n = 4)	P value
Age (years)	58 ± 18.4	63 ± 20.6	NS
Male	6/7 (86%)	3/4 (75%)	NS
Ejection fraction (%)	47 ± 14.2	34 ± 25.4	NS
Dose of epinephrine [mg]	5 ± 4.7	9 ± 2.3	NS
Dose of lidocaine [mg]	29 ± 48.8	33 ± 57.7	NS
Dose of nifekalant [mg]	17 ± 5.5	16 ± 3.5	NS
Dose of LSGB [mg]	10 ± 3.2	10 ± 0.0	NS
Number of DC shocks	36 ± 75.4	7 ± 3.8	NS
Serum K^+ level [mEq/L]	4.9 ± 1.4	5.5 ± 1.7	NS
Serum pH	7.25 ± 0.15	7.13 ± 0.15	NS
Serum lactate	75.1 ± 54.3	77.3 ± 19.4	NS
Admitted ICU	6/7 (86%)	–	–
Glasgow coma scale	3 ± 1.7	–	–

Values are means ± SD of defibrillation success and failure cases. Data were obtained during cardiopulmonary resuscitation and after successful defibrillation; LSGB — left stellate ganglion block; DC — direct-current cardioversion; ICU — intensive care unit. Significant value $p < 0.05$

survival was estimated by the admission rate to the intensive care unit, and the long term prognosis was evaluated by the Glasgow Outcome Scale. In the defibrillation success cases by LSGB, both the short-term and long-term prognoses were superior and complete recovery was achieved by 2 patients (Table 2: Case 1 and 6). LSGB was performed by a cardiologist in 7 cases, by a critical care practitioner in 3 cases, and by the anesthesiologist in 1 case.

Background of the 11 patients in LSGB group and the therapeutic outcome (Table 2)

The baseline characteristics of the 11 patients with respect to the CPR implementation and the therapeutic outcomes are shown in Table 2. Where there was underlying disease, reference was made to the patient's record at our hospital, the primary home doctor and information from the family. All the 11 patients had primary cardiac disease, and there was no exogenous factor related to CPA. The underlying diseases included old myocardial infarction (OMI, 2 patients), acute myocardial infarction (AMI, 3 patients), hypertrophic cardiomyopathy (HCM, 2 patients), hypertension (HT, 2 patients), dilated cardiomyopathy (DCM, 1 patient), chronic heart failure (CHF) with severe aortic valve regurgitation (AR, 1 patient), and pulmonary hypertension (PH, 1 patient). The drug used for LSGB was

Table 2. Background of the 11 patients in LSGB group and the therapeutic outcome.

Patient no.	Underlying disease	Defibrillation success	LSGB/dose [ml]	Diameter of [mm] pupil (right/left) Pre ➔ Post LSGB	Onset and course	VT/VF rate [bmp]
1	OMI	+	B/10 + M/10	4/4 → 4/3	VT → VF → SR	230–250
2	AMI	+	B/10	4/4 → 4/3	VT → VF → SR	240–250
3	HCM	+	B/10	5/5 → 5/3	VT → VF → SR	200–220
4	HCM	+	L/10 + R/10	5/5 → 5/2	VT → VF → SR	240–280
5	AMI	+	B/10	6/6 → 6/3	VF → VT → SR	230–260
6	AMI	+	L/5	8/8 → 8/3	VF → SR	250–280
7	HT	+	B/10	8/8 → 8/3	VF → SR → Asystole	260–280
8	DCM	–	L/15	5/5 → 5/5	VF → PEA → Asystole	230–240
9	OMI	–	B/10	6/6 → 6/6	VF → PEA → Asystole	260–280
10	AR, CHF	–	R/10	5/5 → 5/5	VF → PEA → Asystole	260–280
11	PH	–	B/10	5/5 → 5/5	PEA → VF → Asystole	220–240

OMI — old myocardial infarction, AMI — acute myocardial infarction, HCM — hypertrophic cardiac myopathy, HT — hypertension, DCM — dilated cardiac myopathy, AR — aortic valve regurgitation, CHF — chronic heart failure, PH — pulmonary hypertension, LSGB — left stellate ganglion block, B — bupivacaine hydrochloride, M — mepivacaine hydrochloride, L — lidocaine hydrochloride, R — ropivacaine hydrochloride, VF — ventricular fibrillation, VT — ventricular tachycardia; SR — sinus rythm; PEA — pulseless electrical activity

ropivacaine hydrochloride in 2 cases, mepivacaine hydrochloride in 1 case, lidocaine hydrochloride in 3 cases and bupivacaine hydrochloride in 7 cases (including duplicate use). The therapy response of LSGB was identical to one of the symptoms of Horner's syndrome. Prompt miosis of the left eye suggested successful LSGB. The occurrence of ipsilateral miosis was fortunately easy to recognise since both pupils were quite dilated in the out-of-hospital CPA patients before LSGB was performed.

One of the patients from the success group, a 22-year-old male suffering from cardiomyopathy was treated 207 times with DC cardioversion in combination with PCPS. This was the first case of LSGB in this study and was therefore performed by a skilled anesthesiologist, and defibrillation was finally successful. On the other hand, ipsilateral miosis was never observed in any of the 4 cases in the failed group. The reasons were thought to be as follows. It was difficult to obtain the blocking effect in 1 patient (Case 8) because of an anatomical change following cervical lymphadenectomy. In 2 other cases (Cases 9 and 10) sudden cardiac arrest occurred following LSGB, and they never reverted to spontaneous circulation. The reason was not clear, but the slight inotropic action of LSGB may have had some effect, because these 2 patients had severe heart failure owing either to OMI or massive AR. The remaining 1 patient (Case 11) showed the worst acidosis on arrival of all the cases and a sinus suppression effect might have developed owing to the cross-interaction of LSGB under conditions of acidosis. From these 4 cases, as for LSGB, it appears that an unfavourable action may possibly develop where there is severe cardiac dysfunction and acidosis.

An example of a case who demonstrated complete recovery owing to the combined therapy of NIF and LSGB (Fig. 3, 4)

In October 2006 an 82-year-old male with recurrent VT/VF was admitted to our Emergency Department. Since he had a past history of CPA due to MI, an implantable cardioverter-defibrillator (ICD) had been inserted in another hospital. Prior to his being transferred to our hospital, VT/VFs had automatically been detected and ICD shocks actuated 7 times. All these DC shocks had succeeded in converting the sinus rhythm, and his circulatory condition was therefore stable on arrival (Fig. 3A). LID was used as a first-line drug because QT was already slightly prolonged following the oral intake of AMD (Fig. 3, upper panel of ECG). LID was administered step by step (50 mg + additional 50 mg),

and sinus rhythm was restored temporarily (Fig. 3A). NIF was then administered (0.15 mg/kg) as a second-line agent, although its effect in preventing VT/VF was also temporary. Soon afterwards VT/VF recurred frequently and deteriorated into ES. Following the use of drug sedation (1% propofol) with tracheal intubation, additional NIF (0.15 mg/kg) was administered (Fig. 3B). Since the preventive effect of sedation on VT/VF lasted only 30 min, LSGB was performed by stepwise injection of 0.25% bupivacaine (5 mg + additional 5 mg). Bupivacaine was not sufficient to develop the blocking effect but, owing to the change to 1% mepivacaine from bupivacaine, sinus rhythm was soon restored. Although VT/VF recurred after 1 hour, the combined therapy of LSGB using mepivacaine and NIF (0.15––0.3 mg/kg, *i.v.*) finally succeeded in maintaining sinus rhythm. Although the QTc-prolongation effect of NIF was never obtained by a single administration of NIF along with sedation, the QTc was significantly prolonged after administration of intravenous NIF along with LSGB (Fig. 4).

Discussion

The major findings of the present study are as follows: (1) the combined use of NIF and LSGB was useful in the treatment of NIF-resistant VT/VF in patients with out-of-hospital CPA (defibrillation effect: 64%, n = 11), (2) the admission rate and prognosis were superior in the LSGB group compared with the non-LSGB group, (3) there were no significant differences in patient characteristics and CPR content between the defibrillation success and failure subgroups in the LSGB group.

Intravenous class III anti-arrhythmic agents: differences between AMD and NIF

NIF is a pure IKr-channel blocker that was originally developed by Mitsui Pharmaceutical Company, since the use of intravenous AMD is still not allowed in Japan. AMD has established an immovable position as a first-line drug of CPR based on AHA guidelines (evidence level: class IIb) in emergency situations in all countries except Japan [13]. It is a multiple-channel blocker and has an extremely superior defibrillation effect by means of its various pharmacological actions in addition to the IKr-channel blocking action [14]. However, it has also been reported that intravenous AMD had side effects such as conduction disturbance and hypotension caused by its calcium channel blocking, sodium channel blocking and beta blocking actions [15].
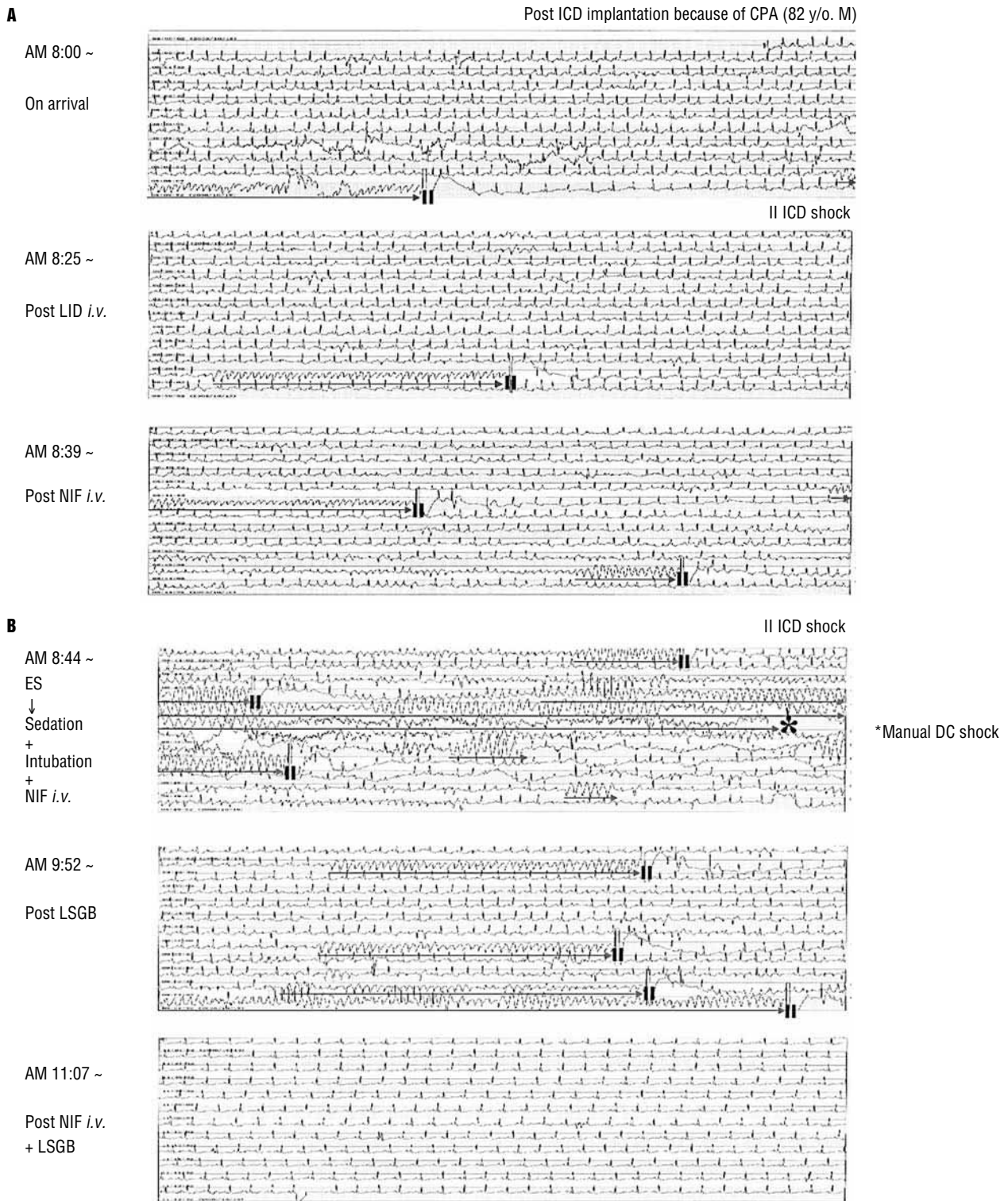
A

Post ICD implantation because of CPA (82 y/o. M)

AM 8:00 ~

On arrival

II ICD shock

AM 8:25 ~

Post LID *i.v.*

AM 8:39 ~

Post NIF *i.v.*

B

II ICD shock

AM 8:44 ~
ES
↓
Sedation
+
Intubation
+
NIF *i.v.*

*Manual DC shock

AM 9:52 ~

Post LSGB

AM 11:07 ~

Post NIF *i.v.*
+ LSGB

Figure 3. Recordings of the electrocardiograph of implantable cardioverter-defibrillator (ICD) in patients with inferior myocardial (MI) patient. Eighty two year old male with recurrent ventricular tachycardia/ventricular fibrillation (VT/VF) was admitted to our emergency department. VT/VFs were automatically detected and ICD shocks were actuated 7 times. Lidocaine (LID) was used as a first-line drug because QT was already slightly prolonged following oral intake of amiodarone (AMD), and sinus rhythm was restored temporarily (**A** — middle panel). Then, nifekalant chydrohloride (NIF) was administered as a second-line agent; however, its effect was also temporary (**A** — lower panel). Soon after, VT/VF deteriorated into electrical storm (ES) (**B** — top panel). Following the use of drug sedation, additional NIF was administered. Then left stellate ganglion block (LSGB) was performed, and sinus rhythm was restored, however its effect was for 60 min (**B** — middle panel). Finally combined therapy of NIF and LSGB succeeded maintaining the sinus rhythm (**B** — lower panel).
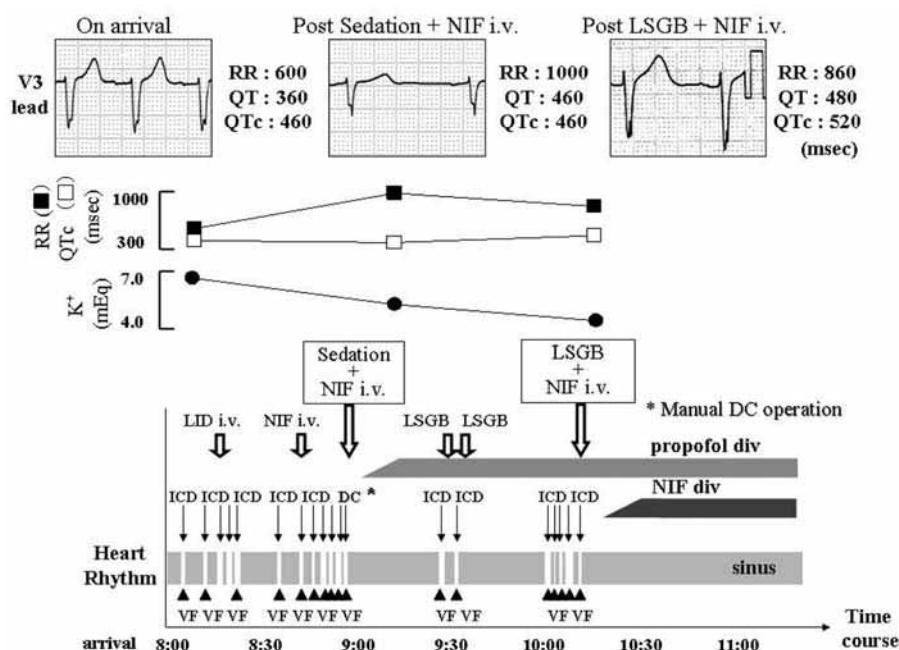
Figure 4. Clinical time course of cardiopulmonary resuscitation (CPR). The upper panel shows the V3 lead of the echocardiograph. The QTc-prolongation effect of nifekalant (NIF) was not obtained by a single application of NIF with sedation, but QTc was significantly prolonged following the combined use of NIF and left stelle ganglion block (LSGB). The middle panel shows the fluctuations in RR intervals, QTc intervals, and serum potassium (K^+) levels. The lower panel shows the schema of the clinical time course (transverse axis) of CPR from the time of arrival to admission.

On the other hand NIF can be used for patients with severe cardiac failure and hemodynamically unstable VT/VF, since it has no negative chronotropic and inotropic actions [1, 2]. From a rat model of heart failure it is known that NIF has a positive inotropic action through the sarcoplasmic reticulum [16]. However, the disadvantage of NIF is that a single use of NIF could not prolong the QT in very rapid VF. The anti-arrhythmic action of NIF depends upon the cycle length of VT/VF, which is known as the reverse frequency dependence effect [3]. Therefore excessive QT prolongation accompanied by bradycardia is potentially dangerous and can cause torsades de pointes [17].

The above-mentioned, pharmacological action is markedly different with AMD and NIF, although they are the same potassium anti-arrhythmic agents. For each medicine adequate knowledge is needed of its concomitant agents and the indications for its use.

The pharmacological effect of NIF on CPA patients

In our previous study the defibrillation efficiency of NIF was compared for patients with out-of-hospital CPA and in-hospital CPA. We observed that the defibrillation efficiency was slightly lower in the out-of-hospital cases than in the in-hospital cases (75% *vs.* 89%) and the QTc prolongation effect in out-of-hospital CPA was less than that in in-hospital CPA (mean QTc, 0.43 ms *vs.* 0.6 ms) [7]. It was difficult to inhibit the IKr currents completely in out-of-hospital CPA because of sympathetic hypertonia by large doses of epinephrine, severe acidosis and hyperkalemia. As shown in Figure 4, because of the occurrence of ES sympathetic hypertonia never provided the QTc-prolongation effect by a single application of NIF even under sedation. However LSGB could enhance the effect of NIF by reducing the sympathetic tone relatively. It should be noted that NIF was never administered exclusively until QT had been prolonged, since the threshold of that curative effect and the drug toxicity of NIF might be in abutment with each other in out-of-hospital CPA. There is a report that the occurrence of torsade de pointes induced by NIF in humans was due not only to excessive QT prolongation but also to the increase in transmural dispersion of repolarisation (TDR) [17]. In other words, there is a possibility that TDR might be increased

where there has been overdosage of NIF, even if QTc is not prolonged. In addition, from the basic studies using normal rabbit hearts one of the defibrillation mechanisms of NIF was explained as the destabilisation effect of the excitement making it difficult to maintain the re-entrant circuit of VT/VF [5]; in other words, NIF not only possesses a strong anti-arrhythmic action but also poses the risk of furthering VF or its recurrence. However, the simultaneous use of NIF and DC cardioversion can aid the termination of VF and prevent the generation of new re-entrant circuits.

Which is better as a sympathetic blockade, intravenous beta-blocker or LSGB?

A stellate ganglion (SG) is one of the cervical sympathetic trunks and is divided into superior, middle, and inferior cervical ganglions. An SG organises and controls the preganglionic fibres of the head, face, neck, arms and chest, along with the cardiac sympathetic supply that innervates the surface of the ventricles [18]. It is known that heterogeneous sympathetic innervation is related to the generation of ventricular arrhythmias and sudden cardiac death [19]. VT/VF could be induced in dogs with MI by administration of the nerve growth factor into the LSG; furthermore, the pathological analysis of excessive sympathetic nerve sprouting might be related to sudden cardiac death [20]. Moreover, it has been revealed that resection of the SG in normal cats significantly reduced the incidence and mortality of VT/VF [21].

There are two methods commonly used for a sympathetic blockade; LSGB or intravenous beta-blocker injection. In *in vivo* experiment propranolol infusion decreased VT/VF vulnerability owing to the attenuation of denervation supersensitivity in dogs after 1–2 weeks of MI [22], while in an extremely acute ischemic model by ligation in dogs dispersion of the refractory period between the ischemic and non-ischemic zones was not reduced by propranolol injection [23]. As for the advantage of an intravenous injection, if the circulatory defect has been sufficiently reversed, it may protect against the effect of deterioration of sympathetic nerve activity on electrical instability during ischemia because a sympathetic blockade effect can be comparatively uniform and little affected by the unevenness of distribution of a cardiac nerve. However, the CPA patient has been under conditions of significant terminal heart failure caused by severe extensive ischemia and sinus suppression because of overwhelming acidosis. The intravenous administration of propranolol is difficult, since it has

stronger inotropic and chronotropic actions than LSGB. The absence of inotropic and chronotropic actions is an advantage of LSGB [12], and therefore it is available for use in CPR. The local sympathetic nerves distributed over the left ventricle are specifically blocked [18]. This makes the cardiac response faster and may promote cardiac effects without producing hemodynamic deterioration.

The efficacy of LSGB and/or NIF with respect to the repolarisation of the left ventricle

Changes in the local dispersion of activation recovery intervals (ARI-Ds) using rabbit hearts that had undergone sympathetic denervation have been investigated by one of the present authors. It was observed that ARI-Ds were significantly increased by the stimulation of LSG in comparison with intravenous beta-stimulants [24]. We hypothesised that LSGB could decrease ARI-Ds, larger than intervenous beta-blocker, and as results, improve the regional conduction block in an ischemic heart. In a healthy volunteer the QT and QTc intervals were shortened, but the RR interval and QT dispersion (QT-D) were not altered by LSGB [25]. The resection of the thoracic sympathetic trunk in a patient with congenital long QT syndrome significantly decreased the QT-D without QT shortening [26]. We speculate that if QT has been excessively extended by the effect of NIF, LSGB may have the potential to correct the QT-D in the drug-induced long QT syndrome.

Blockade of the right stellate ganglion (RSGB) is never recommended for patients with heart disease because of its proarrhythmic effects. In an experimental model the occurrence of episodes of VT/VF was increased by RSGB in occlusion-induced arrhythmias [9]. Even in a healthy volunteer, RSGB produced RR shortening, QT prolongation and exacerbation of QT-D [25] and fluctuations of the vagal tone [27]. The difference between the reactivities of the LSGB and RSGB are thought to be influenced by the expression of beta receptors, the innervation of the sinus node from the RSG and infiltration anesthesia to the cardiac branch of the vagal nerve [27, 28].

As regards electrophysiological examination of NIF, we previously investigated the action potential duration (APD) prolongation effect of NIF using a normal rabbit and reported that NIF decreased the APD dispersion by increasing the homogeneous APD at the surface of the heart [29]. While in the *in vivo* experiment using CPA model due to VT/VF induction in MI dogs, intravenous NIF improved TDR owing to the ARI prolongation of the mid-layer of the left ventricle [30].

From these considerations it appears that the combination of NIF and LSGB has the potential to promote the homogenization of the electrical instability in a diseased heart; nevertheless, further experiments are required for a greater understanding of this therapy.

Conclusion

The combination therapy of intravenous NIF and LSGB was useful in defibrillating intractable VT/VF. The applicability of LSGB for the treatment of refractory VT/VF is not common. It is, however, a potentially innovative treatment strategy for IKr--channel blocker resistant VT/VF.

Study limitations

It was impossible to evaluate RR intervals, QT intervals, QTc intervals and QT-D since with the exception of cases 1 and 4 the ECGs of the patients had revealed VT/VF from the time of arrival until the time of successful defibrillation by LSGB. In cases 1 and 4 LSGB was performed for ES after sedation and therefore the ECG parameters had to be evaluated while keeping in mind the effects of intravenous anesthetic agents.

References

1. Katoh T, Mitamura H, Matsuda N, Takano T, Ogawa S, Kasanuki H. Emergency treatment with nifekalant, a novel class III anti-arrhythmic agent, for life-threatening refractory ventricular tachyarrhythmias: post-marketing special investigation. Circ J, 2005; 69: 1237–1243.

2. Tahara Y, Kimura K, Kosuge M et al. Comparison of nifekalant and lidocaine for the treatment of shock-refractory ventricular fibrillation. Circ J, 2006; 70: 442–446.

3. Nakaya H, Tohse N, Takeda Y, Kanno M. Effects of MS-551, a new class III antiarrhythmic drug, on action potential and membrane currents in rabbit ventricular myocytes. Br J Pharmacol, 1993; 109: 157–163.

4. Murakawa Y, Yamashita T, Kanese Y, Omata M. Can a class III antiarrhythmic drug improve electrical defibrillation efficacy during ventricular fibrillation? J Am Coll Cardiol, 1997; 29: 688–692.

5. Yamazaki M, Honjo H, Nakagawa H et al. Mechanisms of destabilization and early termination of spiral-wave reentry in the ventricle by a class III antiarrhythmic agent, nifekalant. Am J Physiol Heart Circ Physiol, 2007; 292: 539–548.

6. Washizuka T, Chinushi M, Watanabe H et al. Nifekalant hydrochloride suppresses severe electrical storm in patients with malignant ventricular tachyarrhythmias. Circ J, 2005; 69: 1508–1513.

7. Yoshioka K, Amino M, Morita S et al. 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. Circ J, 2006; 70: 21–27.

8. Opthof T, Coronel R, Vermeulen JT, Verberne HJ, van Capelle FJ, Janse MJ. Dispersion of refractoriness in normal and ischemic canine ventricle: effects of sympathetic stimulation. Cardiovasc Res, 1993; 27: 1954–1960.

9. Schwartz PJ, Stone HL, Brown AM. Effects of unilateral stellate ganglion blockade on the arrhythmias associated with coronary occlusion. Am Heart J, 1976; 92: 589–599.

10. Cinca J, Evangelista A, Montoyo J et al. Electrophysiologic effects of unilateral right and left stellate ganglion block on the human heart. Am Heart J, 1985; 109: 46–54.

11. Nademanee K, Taylor R, Bailey WE, Rieders DE, Kosar EM. Treating electrical storm: sympathetic blockade versus advanced cardiac life support-guided therapy. Circulation, 2000; 102: 742–747.

12. Mullenheim J, Preckel B, Obal D et al. Left stellate ganglion block has only small effects on left ventricular function in awake dogs before and after induction of heart failure. Anesth Analg, 2000; 91: 787–792.

13. 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 7.2: Management of Cardiac Arrest IV65. Circulation, 2005; 112: IV58–IV66.

14. Levine JH, Massumi A, Scheinman MM et al. Intravenous amiodarone for recurrent sustained hypotensive ventricular tachyarrhythmias. Intravenous Amiodarone Multicenter Trial Group. J Am Coll Cardiol, 1996; 27: 67–65.

15. Caron MF, Kluger J, White CM. Amiodarone in the new AHA guidelines for ventricular tachyarrhythmias. Ann Pharmacother, 2001; 35: 1248–1254.

16. Endo H, Miura M, Hirose M et al. Reduced inotropic effect of nifekalant in failing hearts in rats. J Pharmacol Exp Ther, 2006; 318: 1102–1107.

17. Ohashi J, Yasuda S, Miyazaki S et al. Prevention of life-threatening ventricular tachyarrhythmia by a novel and pure class-III agent, nifekalant hydrochloride. J Cardiovasc Pharmacol, 2006; 48: 274–279.

18. Janes RD, Brandys JC, Hopkins DA, Johnstone DE, Murphy DA, Armour JA. Anatomy of human extrinsic cardiac nerves and ganglia. Am J Cardiol, 1986; 57: 299–309.

19. Dae MW, Lee RJ, Ursell PC, Chin MC, Stillson CA, Moise NS. Heterogeneous sympathetic innervation in German shepherd dogs with inherited ventricular arrhythmia and sudden cardiac death. Circulation, 1997; 96: 1337–1342.

20. Cao JM, Chen LS, KenKnight BH et al. Nerve sprouting and sudden cardiac death. Circ Res, 2000; 86: 816–821.

21. Kuo JS, Lin NN, Cheng WY, Cheng FC, Chai CY. Effects of reducing sympathetic activities on acute myocardial ischemia in cats. Chin J Physiol, 1993; 36: 101–107.

22. Inoue H, Zipes DP. Results of sympathetic denervation in the canine heart: supersensitivity that may be arrhythmogenic. Circulation, 1987; 75: 877–887.

23. Tanabe T, Takahashi K, Kitada M, Yoshioka K, Handa S, Mori H. Effects of sympathetic stimulation, with and without previous alpha 1 and beta adrenoreceptors blockade, on refractoriness dispersion in canine heart. Cardiovasc Res, 1994; 28: 1787–1793.

24. Yoshioka K, Gao DW, Chin M et al. Heterogeneous sympathetic innervation influences local myocardial repolarization in normally perfused rabbit hearts. Circulation, 2000; 101: 1060–1066.

25. Egawa H, Okuda Y, Kitajima T, Minami J. Assessment of QT interval and QT dispersion following stellate ganglion block using computerized measurements. Reg Anesth Pain Med, 2001; 26: 539–544.

26. Yamashita K, Tomiyasu S, Fujie T et al. Endoscopic resection of the thoracic sympathetic trunk for the treatment of frequent syncopal attack of idiopathic long QT syndrome. Masui, 1999; 48: 399–403.

27 Fujiki A, Masuda A, Inoue H. Effects of unilateral stellate ganglion block on the spectral characteristics of heart rate variability. Jap Circ J, 1999; 63: 854–858.

28. Martins JB, Zipes DP, Lund DD. Distribution of local repolarization changes produced by efferent vagal stimulation in the canine ventricles. J Am Coll Cardiol, 1983; 2: 1191–1199.

29. Amino M, Yamazaki M, Nakagawa H et al. Combined effects of nifekalant and lidocaine on the spiral-type re-entry in a perfused 2-dimensional layer of rabbit ventricular myocardium. Circ J, 2005; 69: 576–584.

30. Yoshioka K, Amino M, Usui K et al. Nifekalant hydrochloride administration during cardiopulmonary resuscitation improves the transmural dispersion of myocardial repolarization. Circ J, 2006; 70: 1200–1207.