Table 3
Patient outcomes according to rescuer's CPR training experience.

	Trained ($n=60$)	Untrained ($n=60$)	p-Value
VF as initial rhythm, n (%)	10(16.7)	5(8.3)	0.135
Pre-hospital ROSC, n (%)	14(23.3)	14(23.3)	1.000
Hospital admission, n (%)	11(18.3)	17(28.3)	0.280
One-month survival, n (%)	8(13.3)	5(8.3)	0.279
Neurologically favorable one-month survival, n (%)	2(3.3)	1(1.7)	0.500

VF denotes ventricular fibrillation; ROSC, return of spontaneous circulation.

tional CPR training programs is one of the major inhibiting factors for its wider dissemination.[34] A short and efficient training program such as CPR course using a video-self learning materials,[32,33] personal manikin,[33] or simplified chest-compression only CPR[14–16] should be considered to increase the chance for lay rescuers to acquire CPR skills. Interestingly, patients with witnessed arrest were less likely to receive bystander CPR. One potential explanation for this paradox may be patients' agonal breathing in the early stage of cardiac arrest, which is observed in nearly half of witnessed cardiac arrests[35,36] and can easily mislead rescuers about patient vital states.[27,35,37] Other multiple reasons (e.g., panic, fear of failure, embarrassment and so on) could decrease the willingness of bystanders to start CPR as Swor et al. pointed out.[13] Improvements in the contents of CPR training program such as the recognition of agonal breathing should also be taught to increase CPR, as the 2010 ILCOR statement and AHA Guidelines indicated.[38,39]

In this study, interviews were not completed for 50 rescuers. Among them, 19 rescuers (38%) performed bystander CPR at the arrest scene and 2 (4%) patients survived one month after OHCAs. However, none survived with a neurologically favorable outcome. The proportion of bystander CPR among the people who could not be interviewed was lower than the rescuers who completed the interviews. If the persons who did not perform CPR were less trained and prone to refuse the interview, our study results might underestimate the effectiveness of CPR training.

This study has some other limitations. First, data on the quality of bystander CPR were unknown in this study. Second, bystander information was obtained by interviewing the bystanders themselves, and some recall bias might exaggerate our study results, although the interviews at the arrest scenes were conducted with great care. Third, although we adjusted for some possible confounding factors including patient's and rescuer's age and sex and rescuer's occupation (health professionals or not), there might still be unmeasured but influential confounding factors.

5. Conclusions

This study showed that rescuers who had CPR training were more willing to perform CPR at the OHCA scenes than those who had not. Because CPR by bystander is strongly linked to improved patient survival, CPR training could yield better outcomes after OHCA. Further studies are needed to prove the effectiveness of CPR training on survival.

Conflict of interest

There are no conflicts of interest to declare in relation to this manuscript.

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Is There an Evening Peak in the Occurrence of Out-of-Hospital Cardiac Arrest in Japanese?

– Special Situations With Circadian Variation –

Hiroshi Nonogi, MD, PhD

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EDITORIAL

Is There an Evening Peak in the Occurrence of Out-of-Hospital Cardiac Arrest in Japanese?

– Special Situations With Circadian Variation –

Hiroshi Nonogi, MD, PhD

In this issue of the Journal, Tsukada et al show circadian variation in out-of-hospital cardiac arrests, with peaks in the morning and the evening, and report that aging affects the circadian variation, especially in very elderly patients, who show a predominance of events in the evening.[1]

Article p1880

Sudden cardiac death is the leading cause of death in industrialized countries, accounting for 10–20% of total mortality, and circadian rhythms have been described for acute myocardial infarction (AMI) and sudden death.[2] A morning peak in occurrence is well-documented for both these events,[3–7] and it begins after subjects assume an upright posture and start the day's activities, during a time of sympathetic nervous system activation. Beta-blocker therapy significantly reduces the incidence of sudden cardiac arrest. Clinical observations suggest a close association between ventricular arrhythmia and sympathetic activity.[8]

Another mechanism of the circadian variation in AMI is the morning increase in the incidence of plaque rupture.[9] Rupture of an atherosclerotic plaque with subsequent coronary thrombosis is the most common underlying pathophysiologic mechanism of sudden death,[7] and plaque rupture in the early morning has been associated with an increase in the prothrombotic state via an elevation of the thrombin–antithrombin complex and a higher level of lipoprotein (a).[10]

Several reports from Japan have shown a circadian variation in both AMI, with peaks in the early morning and the evening,[11,12] and sudden cardiac arrest.[13,14] Hayashi et al reported that a circadian variation with 2 peaks, between 6 and 8 am, and between 6 and 8 pm, was characteristic of sudden cardiac arrest.[13] However, the precise mechanisms for the peak incidence in the evening have been unknown.

Tsukada et al show that the circadian pattern of sudden death in the evening appeared to be more pronounced in older patients, who had more cardiac arrests at home, especially in the lavatory and the bathroom, than younger patients.[1] These authors also show a seasonal variation, with more frequent occurrence of sudden death in the winter than in other seasons. They suggest a risk for sudden cardiac arrest with prolonged hot bathing and physical movement in the bathroom. In Japan, hot bathing, the water pressure and the lower temperature in the bathroom might be risks for cardiovascular events.

Thus, the study by Tsukada et al is important to our understanding of the pathophysiology of sudden cardiac arrest in Japan and for establishing treatment and prevention of cardiovascular events. Their study included quite a large number of patients, although the data come from a local cohort of patients in a single center. However, Japanese physicians can now analyze a prospective, nationwide, population-based registry of out-of-hospital cardiac arrest using the standardized Utstein style. Kitamura et al have reported the effect of a nationwide public-access defibrillation program using more than 300,000 patients' data.[15] By using large population-based databases, more precise analysis of circadian variation in Japan is possible, especially in older patients who have out-of-hospital cardiac arrests. Such data will also contribute to preventing or improving the treatment of out-of-hospital cardiac arrest worldwide.

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Reduction in incidence and fatality of out-of-hospital cardiac arrest in females of the reproductive age

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Aims The aim of this study was to determine relative risk (RR) of incidence and fatality of out-of-hospital cardiac arrest (OHCA) by gender and oestrogen status.

Methods and results In a prospective, population-based observational study from 1998 through 2007, incidence and neurologically intact 1-month survival after OHCA were compared by gender after grouping: 0–12 years, 13–49 years, and ≥50 years according to menarche and menopause age. Among 26 940 cardiac arrests, there were 11 179 females and 15 701 males. Age-adjusted RR of females for OHCA incidence compared with males was 0.72 [95% confidence interval (CI), 0.58–0.91] in age 0–12 years, 0.39 (95% CI, 0.37–0.43) in age 13–49 years, and 0.54 (95% CI, 0.52–0.55) in age ≥50 years. Females aged 13–49 years had a significantly higher good neurological outcome than males [adjusted odds ratio (OR), 2.00 (95% CI 1.21–3.32)]. This sex difference was larger than that in the other age groups [adjusted OR, 0.82 (95% CI, 0.06–12.02) in age 0–12 years and 1.23 (95% CI, 0.98–1.54) in age ≥50 years].

Conclusion Reproductive females had a lower incidence and a better outcome of OHCA than females of other ages and males, which might be explained by cardioprotective effects of endogenous oestrogen on OHCA.

Keywords Out-of-hospital cardiac arrest • Sudden death • Cardiopulmonary resuscitation • Epidemiology • Gender • Women

Introduction

Sudden cardiac arrest (SCA) is the leading cause of death in the industrialized world,[1] and approximately 50 000 events occur every year in Japan.[2] Females are generally less likely to die of cardiovascular disease than males,[3,4] and there are age-related differences in incidence and outcomes of SCA in males and females.[5–10] But the aetiology of gender-related differences in cardiac arrest remains to be determined.

Animal models of cardiac arrest suggest that acute doses of oestrogen are associated with a good prognosis after cardiac arrest.[11,12] Although some protective effects of oestrogen on the cardiovascular system have been suggested,[13–17] no clinical studies have assessed the gender differences in incidence and outcomes of SCA by focusing on oestrogen exposure of females.

The Utstein Osaka Project is a large prospective population-based cohort study of out-of-hospital cardiac arrests (OHCAs) in Osaka, Japan, which covered about 8.8 million residents and

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was launched in 1998.[5,18,19] During the initial 9 years and 8 months, there were 29 192 emergency medical service (EMS)-resuscitated OHCAs of presumed cardiac aetiology. Our hypothesis is that endogenous oestrogen has protective effects on OHCA incidence and outcome in this population.

Methods

Study design, setting, and population

This observational study enrolled all patients who suffered OHCA of presumed cardiac aetiology before EMS arrival, were treated by EMS, and were transported to medical institutions in Osaka Prefecture from 1 May 1998 through 31 December 2007. Osaka is the second largest prefecture in Japan with a population of 8 805 081 inhabitants in an area of 1892 km^2. The census population included 4 293 763 males and 4 495 591 females, and the proportion of people aged 65 years and over is 14.9% in 2000.[20] Cardiac arrest was defined as the cessation of cardiac mechanical activity as confirmed by the absence of signs of circulation.[21] The arrest was presumed to be of cardiac aetiology unless it was caused by trauma, drowning, drug overdose, asphyxia, exsanguinations, or any other non-cardiac causes. These diagnoses were determined by the physician in charge in collaboration with the EMS rescuers.

The research protocol was approved by the institutional review board of Osaka University with the assent of the EMS authorities of the local governments in Osaka Prefecture.

Emergency medical service systems in Osaka

In Osaka Prefecture, there are 35 fire stations with emergency dispatch centres. The EMS system is operated by the local fire stations. The free telephone emergency number 119 is used to call for ambulance from anywhere in Japan. Emergency services are provided 24 h each day by them, which are single tiered in 33 stations and two tiered in two stations. The latter uses medics followed by physicians. The most highly trained pre-hospital emergency care providers are the emergency life-saving technicians (ELSTs). When called, an ambulance is dispatched from the nearest fire station. Usually, each ambulance has a crew of three emergency providers including at least one ELST. They were allowed to insert an intravenous line and an adjunct airway, and to use a semi-automated external defibrillator for OHCA patients during the study period. Specially trained ELSTs were permitted to insert tracheal tubes after July 2004 and administer intravenous epinephrine after April 2006. The use of automated external defibrillators by citizens was legally approved in July 2004. Do-not-resuscitate orders or living wills are not generally accepted in Japan. Emergency medical service providers are not permitted to terminate resuscitation in the field. Therefore, all patients with OHCA who were treated by EMS personnel were transported to hospital and registered in this study. Details of the EMS system in Osaka were described previously.[18]

Data collection and quality control

Data were prospectively collected using a form that included all core data recommended in the Utstein-style reporting guidelines for cardiac arrests.[21] Initial rhythm was recorded and diagnosed by the EMS personnel with semi-automated defibrillators on the scene, and confirmed by the physician who was responsible for the on-line medical direction. The time of EMS call receipt and vehicle arrival at the scene was recorded automatically at the dispatch centre. The time of collapse and initiation of bystander CPR was obtained by EMS interview with the bystander before leaving the scene. The time of defibrillation was recorded in the semi-automated defibrillator.

The data form was filled out by the EMS personnel in cooperation with the physicians in charge of the patient, transferred to the Information Center for Emergency Medical Services of Osaka, and then checked by the investigators. If the data sheet was incomplete, the relevant EMS personnel were contacted and questioned, and the data sheet was completed.

All survivors were followed up for up to 1 month after the event by the EMS personnel and investigators with the cooperation of the Osaka Medical Association and medical institutes in this area. Neurological outcome was determined by a follow-up telephone interview 1 month after successful resuscitation, using the cerebral performance category (CPC) scale: category 1, good cerebral performance; category 2, moderate cerebral disability; category 3, severe cerebral disability; category 4, coma or vegetative state; and category 5, death.[21]

Key group definition and main outcome measures

To assess our hypothesis that endogenous oestrogen would influence OHCA incidence and their outcomes, we divided the patients into the following three groups: 0–12 years, 13–49 years, and 50 years and over according to the published data on mean age of menarche (12.2 $\pm$ 0.9 years) and menopause (49.5 $\pm$ 3.5 years) among Japanese females.[22,23] According to this criterion, females aged 13–49 years would be considered to be exposed to endogenous oestrogen. The primary outcome measure was annual incidence and neurologically intact 1-month survival. Age-adjusted annual incidence of EMS-treated OHCA of presumed cardiac aetiology by gender were calculated by the direct method using 2000 census data and 1985 Japanese model population.[20,24] Neurologically intact outcome was defined as CPC category 1 or 2.[21] Secondary outcome measures included return of spontaneous circulation (ROSC), admission to hospital, and 1-month survival.

Statistical analysis

Patient characteristics were compared between groups using unpaired t-test for numerical variables, and χ^2 test or Fisher's exact test for categorical variables. The relative risk (RR) and its 95% confidence interval (CI) of females against males for the incidence were calculated with the Mantel–Haenszel statistic stratifying by 5-year age stratum. Multiple logistic regression analysis assessed the factors associated with better neurological outcome, and odds ratios (ORs) and their 95% CIs were calculated. As potential confounders, factors that were biologically essential and considered to be associated with clinical outcomes were taken in the multivariable analyses. These variables included age, gender, bystander witnessed status, location of arrest, activity of daily living before arrests, bystander CPR status, first recorded rhythm, time interval from call to the initiation of CPR by EMS personnel, and year of arrest. The interaction between gender and age group on outcomes was also calculated. All of the tests were two-tailed and a P-value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS statistical package ver16.0J (SPSS, Inc., Chicago, IL, USA).

Results

Figure 1 shows an overview of the study patients based on the Utstein template. A total of 53 526 OHCAs were documented during these 9 years and 8 months. Resuscitation was attempted in 50 119, and 29 192 of them were presumed of cardiac aetiology.

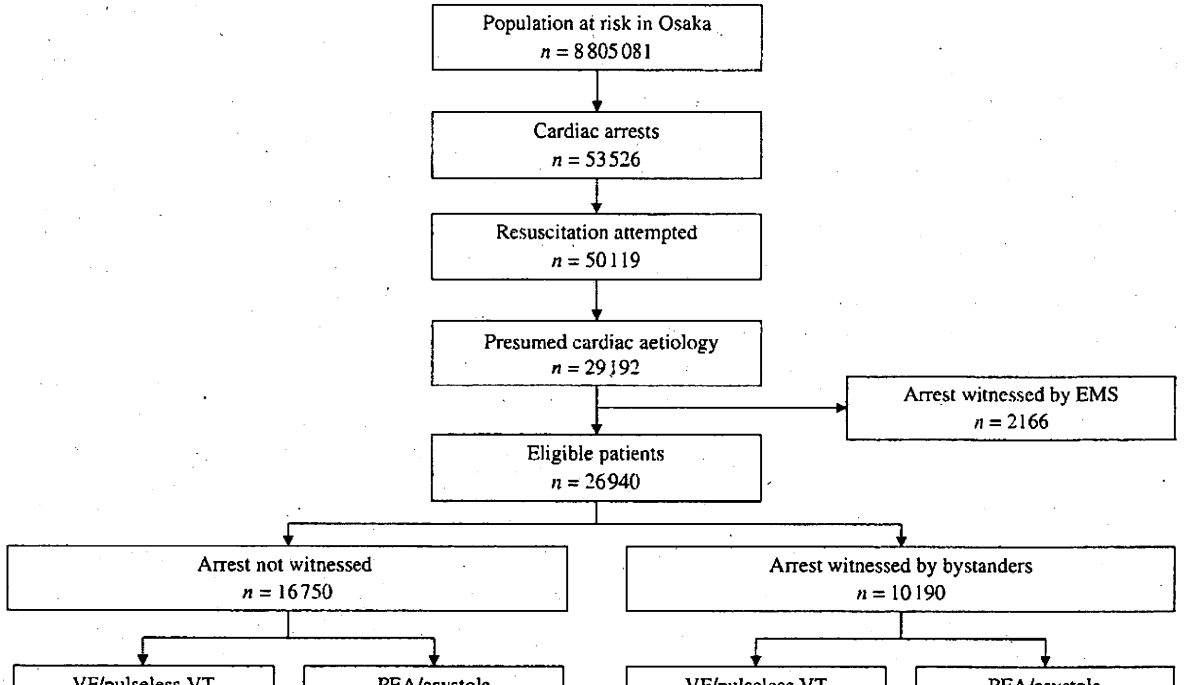

Figure 1 Overview of emergency medical service-treated cardiac arrests with an abridged Utstein template from 1 May 1998 through 31 December 2007. EMS, emergency medical service; VF, ventricular fibrillation; VT, ventricular tachycardia; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; CPC, cerebral performance category.

Excluding 2166 victims who were witnessed by EMS, 26 940 were eligible for our analyses. Among them, 15 701 (58.3%) were males, 11 179 (41.6%) were females, and the remaining 60 (0.2%) were missed for gender. Of these victims, 10 190 were witnessed by bystanders, and 16 750 were not. Among witnessed cases, 2050 had ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT), and 8023 had pulseless electrical activity (PEA) or asystole. Among non-witnessed cases, 845 had VF or pulseless VT and 15 754 PEA or asystole. We could not obtain neurologically intact 1-month survival data for 13 (0.04%) among 26 940 eligible victims. The proportions of neurologically intact 1-month survival among those with VF or pulseless VT and among those with PEA or asystole were 14.8 and 1.4%, respectively, when witnessed, whereas 6.5 and 0.4%, respectively, when not witnessed.

The characteristics of patients who experienced OHCA of presumed cardiac aetiology are shown in *Table 1*. Females were significantly older than males (mean age, 75.5 ± 16.4 vs. 67.9 ± 16.5 years; $P < 0.001$). The proportions of females in the 0–12 years group, the 13–49 years group, and the 50 years and over group were 127/311 (40.8%), 612/2120 (28.9%), and 10 440/24 449 (42.7%), respectively ($P < 0.001$). Females with cardiac arrest were more likely to have their arrests at home than males, and less likely to be witnessed and have VF as initial rhythm, although these differences are statistically insignificant in the age group of 0–12 years. The mean time intervals from call to CPR were similar between genders in each age group.

The incidence of OHCA increased with advancing age group in a non-linear manner in both genders (*Table 2*). Females had a lower incidence rate than males in every age group. The age-adjusted population-based incidence of OHCA of presumed cardiac aetiology was 32.5 per 100 000 person-years in males and 13.2 in females, and that of witnessed OHCA in males and females was 15.6 and 5.3, respectively. Age-adjusted RR of females for the incidence of OHCA in the group of age 13–49 years was 0.39 (95% CI; 0.37–0.43; $P < 0.001$), which was smaller than that in the group of age 0–12 years (0.72; 95% CI 0.58–0.91, $P = 0.005$) and 50 years and over (0.54; 95% CI 0.52–0.55, $P < 0.001$). In cases of bystander-witnessed OHCA of presumed cardiac aetiology, age-adjusted RRs of females for the incidence in the group of age 0–12 years, 13–49 years, and 50 years and over were 0.67 (95% CI 0.41–1.11, $P = 0.092$), 0.32 (95% CI 0.27–0.37, $P < 0.001$), and 0.45 (95% CI 0.43–0.47, $P < 0.001$), respectively.

Table 1 Characteristics of the study participants by age and gender

Characteristic	Age 0–12 years			Age 13–49 years			Age 50 years and over		
	Female (n = 127)	Male (n = 184)	P	Female (n = 612)	Male (n = 1508)	P	Female (n = 10 440)	Male (n = 14 009)	P
Age (years)	1.7 (3.1)	2.0 (3.2)	0.419	37.5 (9.3)	38.1 (9.3)	0.217	78.7 (11.1)	72.0 (11.9)	<0.001
Arrest witnessed by bystanders	19.7 (25)	21.2 (39)	0.777	36.9 (226)	46.8 (705)	<0.001	33.6 (3505)	40.5 (5668)	<0.001
Location of arrest									
Home	92.1 (116)	88.6 (163)		77.0 (470)	59.6 (894)		75.1 (7823)	70.4 (9836)	
Public space	4.0 (5)	4.9 (9)		11.3 (69)	19.9 (299)		5.8 (609)	14.4 (2009)	
Work place			0.732	2.0 (12)	9.4 (141)	<0.001	0.5 (56)	3.7 (512)	<0.001
Health care facility[a]	0.0 (0)	1.1 (2)		2.1 (13)	0.5 (7)		14.5 (1516)	4.8 (673)	
Other	4.0 (5)	5.4 (10)		7.5 (46)	10.7 (160)		4.0 (417)	6.7 (936)	
Activity of daily living before arrests									
Good	73.6 (92)	77.8 (140)		81.2 (492)	84.4 (1257)		63.0 (6524)	72.1 (10 024)	
Disability	20.0 (25)	17.8 (32)	0.647	12.2 (74)	6.8 (101)	<0.001	33.6 (3481)	20.7 (2879)	<0.001
Unknown	6.4 (8)	4.4 (8)		6.6 (40)	8.8 (131)		3.5 (358)	7.2 (1006)	
Type of bystander CPR									
No CPR	51.6 (65)	52.8 (92)		66.7 (405)	67.9 (1017)		65.7 (6826)	72.0 (10 049)	
Chest compression-only CPR	9.5 (12)	6.1 (11)	0.535	12.5 (76)	14.2 (212)	0.244	15.1 (1570)	13.6 (1890)	<0.001
Conventional CPR	38.9 (49)	41.1 (74)		20.8 (126)	17.9 (268)		19.2 (2001)	14.4 (2009)	
Type of initial rhythm									
VF or pulseless VT	2.4 (3)	3.9 (7)		12.5 (76)	23.0 (344)		5.7 (588)	13.4 (1873)	
PEA	11.4 (14)	14.5 (26)	0.467	12.5 (76)	10.1 (151)	<0.001	17.5 (1817)	17.7 (2471)	<0.001
Asystole	85.4 (105)	81.6 (146)		74.8 (456)	66.6 (997)		76.4 (7930)	68.4 (9533)	
Other	0.8 (1)	0.0 (0)		0.3 (2)	0.3 (5)		0.5 (50)	0.4 (50)	
Call to CPR time by EMS personnel (min)	7.5 (2.4)	7.4 (2.6)	0.921	7.9 (2.9)	8.0 (3.1)	0.780	7.8 (3.0)	7.8 (3.1)	0.961

Data are mean (SD) and % (n).

CPR, cardiopulmonary resuscitation; EMS, emergency medical system; VF, ventricular fibrillation; VT, ventricular tachycardia; PEA, pulseless electrical activity.

[a]Health care facility includes chronic facilities and medical clinics.

Table 2 Annual incidence of out-of-hospital cardiac arrest by age and gender

	0–12 years	P	13–49 years	P	50 years and over	P
Female						
Number of victims/population at risk	127/526 398		612/2 193 247		10 440/1 775 946	
Age-adjusted incidence rate per 100 000 population	2.4		3.8		50.1	
Male						
Number of victims/population at risk	184/551 328		1508/2 200 452		14 009/1 541 983	
Age-adjusted incidence rate per 100 000 population	3.3		9.7		98.5	
Adjusted RR of the incidence for female vs. male (95% CI)[a]	0.72 (0.58–0.91)	0.005	0.39 (0.37–0.43)	<0.001	0.54 (0.52–0.55)	<0.001

RR, relative risk; CI, confidence interval.
[a]RRs are adjusted for age, and estimated by the Mantel–Haenszel statistic.

Table 3 Outcomes after out-of-hospital cardiac arrest by age and gender

Outcomes	Age 0–12 years (female = 127, male = 184)	P	Age 13–49 years (female = 612, male = 1508)	P	Age 50 years and over (female = 10 440, male = 14 009)	P	Interaction P[c]
ROSC							
Female	22.0 (28)		26.3 (161)		23.6 (2465)		<0.001
Male	19.6 (36)		20.2 (305)		26.8 (3751)		
Crude OR[a] (95% CI)	1.16 (0.67–2.03)	0.595	1.40 (1.13–1.75)	0.003	0.85 (0.80–0.90)	<0.001	
Adjusted OR[b] (95% CI)	1.35 (0.72–2.54)	0.404	1.90 (1.49–2.44)	<0.001	1.02 (0.95–1.09)	0.385	
Admission							
Female	16.5 (21)		21.6 (132)		17.3 (1810)		<0.001
Male	16.3 (30)		15.9 (240)		19.9 (2788)		
Crude OR[a] (95% CI)	1.02 (0.55–1.87)	0.957	1.45 (1.15–1.84)	0.002	0.84 (0.79–0.90)	<0.001	
Adjusted OR[b] (95% CI)	1.06 (0.53–2.13)	0.990	2.09 (1.60–2.72)	<0.001	1.05 (0.98–1.13)	0.102	
Survival at 1 month							
Female	2.4 (3)		7.4 (45)		3.4 (360)		0.037
Male	4.9 (9)		7.8 (118)		5.2 (733)		
Crude OR[a] (95% CI)	0.47 (0.13–1.77)	0.265	0.94 (0.65–1.34)	0.719	0.65 (0.57–0.74)	<0.001	
Adjusted OR[b] (95% CI)	0.49 (0.11–2.08)	0.344	1.57 (1.05–2.36)	0.026	1.19 (1.03–1.37)	0.019	
Neurologically intact 1-month survival							
Female	1.6 (2)		4.9 (30)		1.3 (139)		0.020
Male	1.6 (3)		4.4 (67)		2.2 (312)		
Crude OR[a] (95% CI)	0.97 (0.16–5.18)	0.969	1.11 (0.71–1.72)	0.641	0.59 (0.48–0.73)	<0.001	
Adjusted OR[b] (95% CI)	0.82 (0.06–12.02)	0.857	2.00 (1.21–3.32)	0.005	1.23 (0.98–1.54)	0.073	

ROSC, return of spontaneous circulation; OR, odds ratio; CI, confidence interval.
[a]OR is for female vs. male. Data shows % (*n*).
[b]ORs are adjusted for age, bystander witnessed status, location of arrest, activity of daily living before arrests, bystander CPR status, first recorded rhythm, time interval from call to the initiation of CPR by EMS personnel, and year of arrest.
[c]Interaction *P*-values are calculated for evaluating the interaction between gender and age group in outcomes.

Table 3 shows the age-stratified outcomes after OHCA of presumed cardiac aetiology by gender. Among OHCAs of presumed cardiac aetiology, females aged 13–49 years had a significantly higher neurologically intact 1-month survival than males (4.9 vs. 4.4%; adjusted OR, 2.00; 95% CI 1.21–3.32, $P = 0.005$). As for ROSC (26.3 vs. 20.2%; adjusted OR, 1.90; 95% CI 1.49–2.44, $P < 0.001$), admission (21.6 vs. 15.9%; adjusted OR, 2.09; 95% CI 1.60–2.72, $P < 0.001$) and 1-month survival (7.4 vs. 7.8%; adjusted OR, 1.57; 95% CI 1.05–2.36, $P = 0.026$) as secondary outcomes, females aged 13–49 years also showed significantly greater frequencies than males. In the group aged 0–12 years in which only a few patients survived, frequency of neurologically intact 1-month survival of females was similar to that of males (1.6 vs. 1.6%; adjusted OR, 0.82; 95% CI 0.06–12.02, $P = 0.86$). In the

group aged 50 years and over, on univariable analysis, females had poorer outcomes than males. However, on multivariable analysis, females had a greater neurologically intact 1-month survival (1.3 vs. 2.2%; adjusted OR, 1.23; 95% CI 0.98–1.54, $P = 0.073$) and 1-month survival (3.4 vs. 5.2%; adjusted OR, 1.19; 95% CI 1.03–1.37, $P = 0.019$), though the differences were small.

When limiting witnessed OHCA with presumed cardiac aetiology, findings were almost identical as those in the whole OHCA. Neurologically intact 1-month survival in witnessed OHCA of females and males was 8.0 vs. 7.7%, respectively (adjusted OR, 0.83; 95% CI 0.07–8.60, $P = 0.86$) in the group aged 0–12 years, 9.7 vs. 8.2%, respectively (adjusted OR, 2.08; 95% CI 1.16–3.73, $P = 0.006$) in the group aged 13–49 years, and 2.9 vs. 4.2%, respectively (adjusted OR, 1.28; 95% CI 0.98–1.67, $P = 0.080$) in the group aged 50 years and over.

Discussion

This study showed that females of reproductive age had a lower incidence of OHCA and better outcomes than males in a large population. Although many studies have examined gender- and age-related differences in OHCA occurrence and outcome,[5–10] the impact of oestrogen status on gender difference was not fully evaluated in the preceding studies.

This study suggests that endogenous oestrogen is protective against the occurrence of OHCA. The mechanism of how oestrogen works protectively against coronary heart disease including SCA is still unclear. It is reported that oestrogen reduces levels of lipoprotein (a), inhibits oxidation of low-density lipoprotein, and improves vascular function.[16,17] In animal models, oestrogen has cardioprotective effects by binding the oestrogen receptor on vascular cells and producing nitric oxide, which is required for the maintenance and repair of vascular endothelium and dilation of vascular smooth muscle.[25,26] In autopsies of female SCA victims, vulnerable plaques varied by age, and the association between hypercholesterolaemia and coronary plaque rapture was found only in post-menopausal age.[15,27] Our data are consistent with these previous studies and strengthen the evidence that endogenous oestrogen has a protective effect against the occurrence of coronary heart disease.

In addition to the protective effect on the occurrence of OHCA, better outcomes after OHCA in females of the reproductive age were demonstrated. Some experimental studies showed that oestrogen might have cardioprotective effects for cardiac arrest.[11,12] Another report suggested that oestrogen had a possible neuroprotective effect.[28] In an animal experiment, a single low dose of E2, one of the major oestradiols in humans, has neuroprotective effects on CPR after cardiac arrest.[29] These findings suggest the protective effects of endogenous oestrogen against not only the occurrence but also survival after cardiac arrests.

If oestrogen exposure reduces the risk for incidence and fatality of SCA, hormone replacement therapy (HRT) might be effective for reducing the occurrence of OHCA and improving survival after OHCA. Observational studies suggested that post-menopausal HRT reduced CVD and sudden death.[17,30] However, some randomized controlled trials indicated that HRT rather increased overall coronary heart disease risk,[17,31] and HRT is not recommended for the prevention of coronary heart disease.[32] This discrepancy between observational studies and randomized trials is under debate, but it could be partially explained by factors such as the initiation time, dose, and delivery route of HRT, as well as genetics, statin use, and socioeconomic status of the recipients.[17,33,34] Further study on the effect of oestrogen as a new therapeutic approach for OHCA would be needed.

This study also showed a lower incidence of OHCA and better outcomes in females compared with males regardless of the age group. There might be other factors than oestrogen which were associated with lower OHCA occurrence and fatality in females. Cardiovascular disease is a major cause of SCA, and representative risk factors for CVD, such as smoking, hypertension, and diabetes mellitus, partially explain these results because CVD risk factors were less likely to occur in females than in males.[35–38] Some underlying diseases of SCA, such as Brugada syndrome and hypertrophic cardiomyopathy, which are less likely to occur in females, might affect the frequency imbalance of OHCA between genders.[39,40] A heavy alcohol consumption and physical exercise could also confound the lower incidence of SCA in females[41–43] because fewer females drink excess alcohol or exercise vigorously.[38] Unfortunately, no information about a history of smoking, drinking, and physical exercise was available in this study. Androgens and testosterone might also be taken into consideration. Although one study suggested that high androgen levels were associated with an increased risk of CVDs,[44] the effects of male sex hormones on CVDs are left unresolved.[45]

Limitations

This study has some limitations. First, we stratified study patients at ages of 12 and 50 years based on the mean age of menarche and menopause in Japanese females.[22,23] We did not obtain any information on menarche and menopausal status and history of HRT from each female suffering from OHCA. Therefore, we might underestimate the effects of active hormonal status owing to misclassification. However, the prevalence of HRT in Japanese females is <10%, and its influences would be small.[46] Secondly, the presence of CVD and the role of CVD risk factors were not assessed in this study. Thirdly, information about the care after admission was lacking. In-hospital diagnosis (e.g. coronary angiographies) and treatment (e.g. hypothermia) might affect survival after OHCA. Fourthly, data integrity, validity, and ascertainment biases are potential limitations. The data collected by EMS providers included relatively few data points that were easy to attain in an accurate manner at the scene, based on the clear and concise Utstein-style guidelines for reporting cardiac arrest.[21] The uniform data collection, consistent definitions, time synchronization process, and large sample size in the population-based cohort study were intended to minimize these potential sources of bias.

More detailed information about age of menarche and menopause, HRT use, and other potential factors associated with OHCA, including CVD risk factors and in-hospital diagnosis and treatment, and measurement of oestrogen concentration in females suffering from OHCA or interventional trial of HRT, would be needed for better ascertainment of the protective effects of oestrogen on OHCA.

Conclusion

Females in the period between menarche and menopause had a lower incidence and better outcomes of OHCA, which might be explained by cardioprotective effects of endogenous oestrogen on OHCA occurrence and outcome.

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ORIGINAL ARTICLE
Arrhythmia/Electrophysiology

Report From J-PULSE Multicenter Registry of Patients With Shock-Resistant Out-of-Hospital Cardiac Arrest Treated With Nifekalant Hydrochloride

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on behalf of the J-PULSE Investigators

Background: Nifekalant hydrochloride (NIF) is an intravenous class-III antiarrhythmic agent that purely blocks the K^+-channel without inhibiting β-adrenergic receptors. The present study was designed to investigate the feasibility of NIF as a life-saving therapy for out-of-hospital ventricular fibrillation (VF).

Methods and Results: The Japanese Population-based Utstein-style study with basic and advanced Life Support Education study was a multi-center registry study with 4 participating institutes located at the northern urban area of Osaka, Japan. Eligible patients were those treated with NIF because of out-of-hospital VF refractory to 3 or more precordial shocks and intravenous epinephrine. Between February 2006 and February 2007, 17 patients were enrolled for the study. The time from a call for emergency medical service to the first shock was 12 (6–26) min. The time from the first shock to the NIF administration was 25.5 (9–264) min and the usage dose of NIF was 25 (15–210) mg. When excluding 3 patients in whom percutaneous extracorporeal membrane oxygenation was applied before NIF administration, the rate of return of spontaneous circulation was 86% and the rate of admission alive to the hospital was 79%. One patient developed torsade de pointes.

Conclusions: Intravenous administration of NIF seems to be feasible as a potential therapy for advanced cardiac life-support in patients with out-of-hospital VF, and therefore further study is warranted. (*Circ J* 2010; **74:** 2308–2313)

Key Words: Advanced life support; Anti-arrhythmic drugs/therapy; Cardiac arrest; Defibrillation; Ventricular fibrillation

Sudden cardiac death is a major clinical problem, causing 300,000 to 400,000 deaths annually and 63% of all cardiac deaths in USA.[1] Rapid defibrillation for ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT) is the most crucial intervention to improve survival after cardiac arrest. Amiodarone is being used for the acute treatment of out-of-hospital cardiac arrest because it was shown to be effective for shock-resistant VF in the ARREST and ALIVE trials.[2,3]

Editorial p 2285

Nifekalant hydrochloride (NIF) is a class-III antiarrhythmic agent having a pirimidinedione structure with the selective inhibition of the rapid component of the delayed rectifier K^+ current (IKr).[4,5] The major adverse effect of NIF is proarrhythmic torsade de pointes (TdP).[6] As class-III antiarrhythmic agents, NIF and amiodarone are similar but they do have some differences. NIF is characterized as a pure K^+ channel blocker with a minimal negative inotropic effect.[7,8] Although amiodarone has various pharmacological actions, negative inotropic and chronotropic effects via a β-receptor, Na^+- and Ca^{2+}-channel blocking action seems to be disadvantageous, particularly when amiodarone is administered rapidly to a depressed heart.[9] In the ARREST trial, blood pressure was lower and pressor treatment was required more in amioda-

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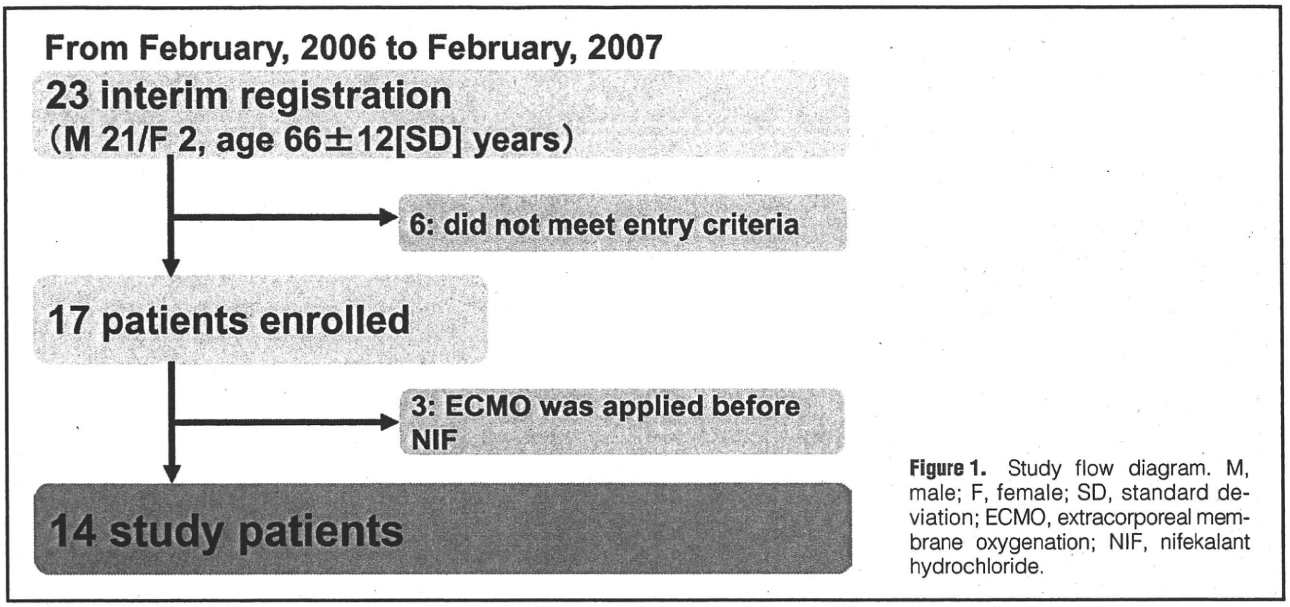

Figure 1. Study flow diagram. M, male; F, female; SD, standard deviation; ECMO, extracorporeal membrane oxygenation; NIF, nifekalant hydrochloride.

rone recipients.[2] Moreover, NIF decreases the defibrillation threshold,[10] whereas amiodarone does not.[11]

On the basis of these unique features of NIF, the present study was designed to investigate the feasibility of NIF as a life-saving therapy to defibrillation for victims of out-of-hospital cardiac arrest.

Methods

Study Design

The J-PULSE (Japanese Population-based Utstein-style study with basic and advanced Life Support Education) study was a multi-center registry study with 4 participating institutes located at the northern urban area of Osaka, Japan; National Cerebral and Cardiovascular Center, Senri Critical Care Medical Center, Mishima Emergency and Critical Care Center, and Osaka University Hospital Trauma and Acute Critical Care Center.

Eligible patients were those treated with NIF because they were adults with electrocardiographically documented out-of-hospital VF, not due to trauma, drowning and acute airway obstruction, or other cardiac rhythms that converted to VF, and because the VF was resistant to 3 counter-shocks, at least 1 dose of intravenous epinephrine, and fourth defibrillator shock. Therapy using NIF did not include the general advice of the Cardiopulmonary Resuscitation and Emergency Cardiovascular Care to administer amiodarone,[12] but instead was used as a replacement for this guideline. NIF was intravenously administered at the dose of 0.15–0.30 mg/kg body weight and then further direct counter-shock was delivered. If VF persisted after further shocks, NIF was additionally used at the dose of 0.15–0.30 mg/kg body weight, and attempts at resuscitation. Percutaneous extracorporeal membrane oxygenation (ECMO)[13] was applied for hemodynamic failure when patients were in refractory cardiac arrest, defined as an absence of return to spontaneous circulation after continuous cardiopulmonary resuscitation (CPR) or in refractory shock, defined as shock not responding to optimal conventional treatment.

This study was approved by the Institutional Review Board, including its provisions for waiver of informed consent. If the patients died, the informed consent was obtained from the family.

Data Recording

Pre-hospital data of the patients' course were prospectively obtained from the ambulance call report in the Utstein-style,[14] including sex, age, initial cardiac rhythm, time course of resuscitation, type of bystander-initiated CPR, return of spontaneous circulation (ROSC) and hospital admission. The times of emergency medical services (EMSs) call receipt and arrival of ambulance car at the scene of cardiac arrest were recorded automatically at EMS center. Data were also obtained from hospital charts, including the prevalence of adverse events of TdP.

Data Analysis

The endpoint in the present study was survival to admission to the hospital. Thus, patients who died in the emergency room were not considered to have been admitted. The endpoint also included ROSC after administration of NIF, which was defined as the documented presence of a measurable pulse and blood pressure. The relationship of clinical and therapeutic variables to survival and ROSC were determined with Fisher's exact test. A value of $P<0.05$ was considered to be statistically significant.

Results

Between February 2006 and February 2007, 23 patients (M 21/F 2, age 66±12 years) were interim registered. From 4 participating institutes (overall annual number of out-of-hospital cardiac arrest, 478; victims of cardiac origin, 173), 15, 5, 2 and 1 patients were enrolled, respectively. Among them, 2 patients did not give informed consent and 4 patients did not meet the entry criteria. Finally, 17 patients (M/F 15/2; median age (range) 68 (46–89) years) were studied in the present study (**Figure 1**). Initial electrocardiogram (ECG) rhythm was VF in 13 patients (76%) and asystole in the remaining 4 patients. A total of 12 patients (71%) were witnessed by a bystander, and 7 patients (41%) received bystander CPR by a witness. A doctor car was used in 11 patients (65%), and ECMO was used in 13 patients (76%).

Table 1. Pt Characteristics and Time Course* of Resuscitation Procedures

Pt	NIF following ECMO	Dr. Car	Age (years)	Sex	Initial ECG rhythm	EMS call from collapse (min)	Arrival of EMS at the scene of collapse (min)	First DC by EMS (min)	Arrival of Dr. Car (min)	No. of DC before hosp. arrival	Use of Epi	Arrival at hosp. (min)	First DC at hosp. (min)	No. of DC after hosp. arrival	NIF (min)	ECMO (min)	ROSC (min)	Death (min)
1	–	–	63	M	VF	–7	4	6	–	9	+	28	30	2	31	–	33	Survived
2	–	–	68	M	VF	–3	9	12	–	6	+	48	50	3	70	75	57	Survived
3	–	–	76	M	VF	–1	5	5	–	8	+	37	40	5	63	–	42	Survived
4	–	+	65	M	VF	NW	4	7	13	4	+	31	34	3	22	52	50	Survived
5	–	+	46	M	Asyst	0	4	26	13	7	+	57	63	2	61	–	–	83
6	–	+	89	M	Asyst	NW	7	14	21	11	+	66	83	2	49	–	73	113
7	–	+	54	F	VF	NW	6	9	17	2	+	26	41	6	42	67	53	Survived
8	–	+	64	M	VF	0	6	9	29	5	+	51	64	3	35	61	93	Survived
9	–	+	81	M	VF	0	3	6	23	5	–	43	227	4	32	244	NR	Survived
10	–	+	56	M	VF	NW	2	19	8	1	+	22	28	2	28	40	40	Survived
11	–	+	74	M	VF	–1	4	8	13	4	+	35	56	4	25	54	–	381
12	–	+	72	M	VF	0	3	14	13	5	+	37	53	2	32	52	52	Survived
13	–	+	71	M	VF	NW	4	6	8	5	+	26	34	3	28	51	88	Survived
14	–	+	60	M	VF	NW	6	10	11	4	+	43	56	2	35	54	56	Survived
15	+	–	78	F	VF	–2	7	19	–	4	+	38	103	5	283	71	–	2,144
16	+	–	64	M	Asyst	–5	4	–	–	0	+	24	47	3	55	53	129	Survived
17	+	–	76	M	Asyst	NW	7	26	–	1	+	26	38	10	49	41	41	Survived

Pt, patient; NIF, nifekalant hydrochloride; ECMO, extracorporeal membrane oxygenation; Dr., doctor; EMS, emergency medical service; DC, direct counter-shocks; hosp, hospital; Epi, epinephrine; ROSC, return of spontaneous circulation; VF, ventricular fibrillation; asyst, asystole; NW, not witnessed; NR, not recorded.
*Time (min) shows the interval from the EMS call.

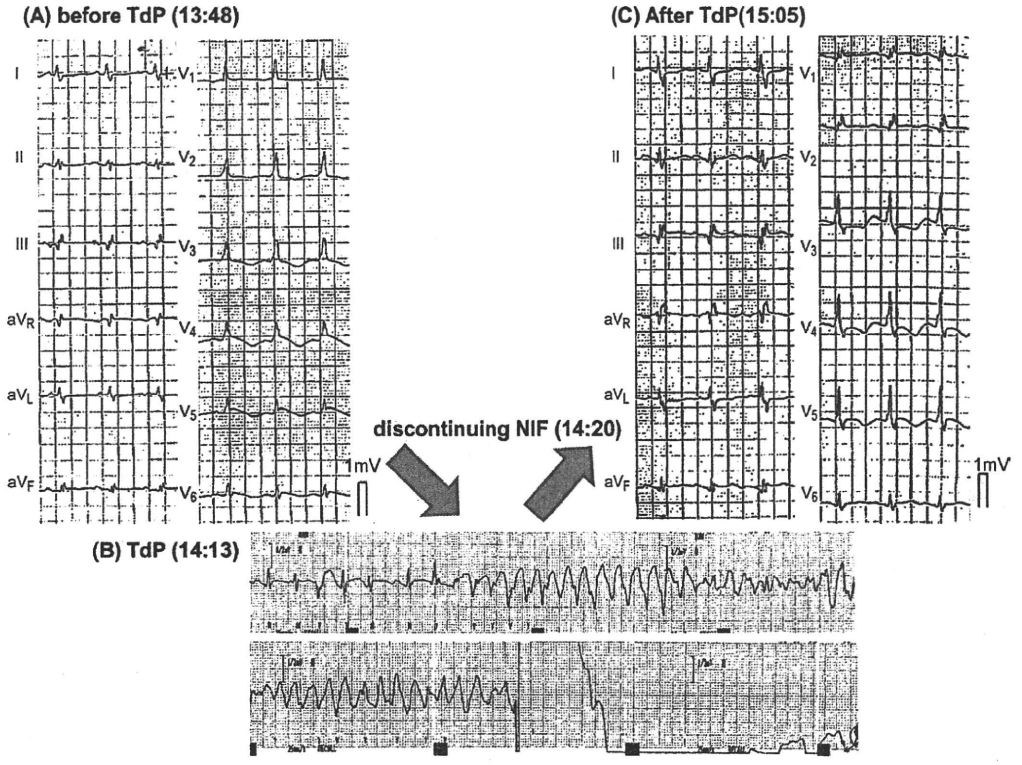

Figure 2. A 76 year-old male patient who survived from out-of-hospital cardiac arrest (Case 3 presented in **Table 1**). After 15mg nifekalant hydrochloride (NIF) was intravenously administered, direct counter-shock successfully terminated ventricular fibrillation. Electrocardiogram (ECG) recorded at 13:48, approximately 1h after ROSC, shows that corrected QT interval (QTc) prolonged to 650ms (**A**). At 14:13, proarrhythmic torsade de pointes (TdP) developed (**B**). The continuous infusion of 0.18mg/kg body weight/h nifekalant hydrochloride was discontinued at 14:20. ECG recorded at 15:05 shows that QTc shortened to 550ms (**C**).

Table 2. Relationship of Clinical and Therapeutic Variables to Survival* and ROSC

Patients	All (n=17)	Exclude ECMO before NIF (n=14)	
	Survival, n (%)	Survival, n (%)	ROSC, n (%)
Age			
65 years≤	7/10 (70.0)	6/8 (75.0)	7/8 (87.5)
<64 years	6/7 (85.7)	5/6 (83.3)	5/6 (83.3)
Gender			
Female	1/2 (50.0)	1/1 (100)	1/1 (100)
Male	12/15 (80.0)	10/13 (76.9)	11/13 (84.6)
Initial cardiac rhythm			
VF	11/13 (84.6)	11/12 (91.7)	11/12 (91.7)
Not VF	2/4 (50.0)	0/2 (0)	1/2 (50.0)
By-stander CPR			
Yes	4/7 (57.1)	3/5 (60.0)	4/5 (80.0)
No	9/10 (90.0)	8/9 (88.9)	8/9 (88.9)
NIF dose			
25–210mg	7/8 (87.5)	6/7 (85.7)	6/7 (85.7)
10–25mg	6/9 (66.7)	5/7 (71.4)	6/7 (85.7)
Epinephrine			
Use	12/16 (75.0)	10/13 (76.9)	11/13 (84.6)
No use	1/1 (100)	1/1 (100)	1/1 (100)
ECMO			
Use	11/13 (84.6)	9/10 (90.0)	9/10 (90.0)
No use	2/4 (50.0)	2/4 (50.0)	3/4 (75.0)

CPR, cardiopulmonary resuscitation. Other abbreviations see in Table 1.
*Survival to admission to the hospital.

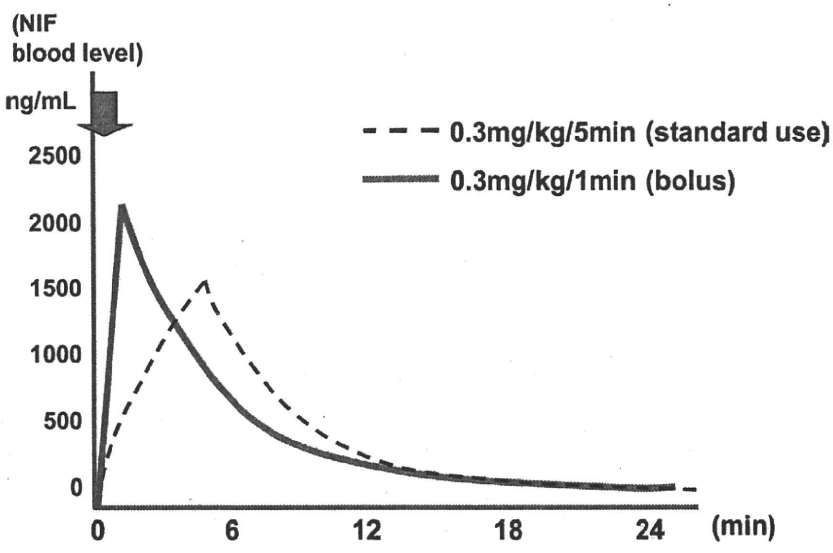

Figure 3. The simulation of the pharmacokinetics of nifekalant hydrochloride (NIF) when the bolus administration at 0.3mg/kg body weight in 1min in comparison with standard use at 0.4mg/kg body weight in 5min.

The characteristics and the time interval from the EMS call in individual patients were summarized in **Table 1**. The median time from a call for EMS to the first shock was 12 (6–26) min. In particular, in patients who were witnessed by a bystander, the median time from the collapse to the EMS call was 1 min. The median time from the first shock to the NIF administration was 25.5 (9–264) min and the median usage dose of NIF was 25 (15–210) mg.

When excluding 3 patients in whom ECMO was applied before NIF administration (**Figure 1**), the rate of ROSC was 86% (n=12 out of 14 patients) and the rate of admission alive to the hospital was 79% (n=11 out of 14 patients). The time from NIF administration to ROSC was within 10 min in 3 patients, 10 to 30 min in 6 patients and over 30 min in 3 patients, respectively (median: 20 min). One ROSC patient died in the emergency room and were not admitted to the hospital. One patient developed TdP (7%), which was transiently induced and disappeared after discontinuing the administration of NIF (**Figure 2**).

We then determined the relationship of clinical and therapeutic variables to ROSC and admission alive (**Table 2**). The rate of admission alive to the hospital was 91.7% in patients in whom initial ECG rhythm was VF, whereas it was 0% in those in whom initial ECG rhythm was asystole (P=0.033). The ROSC rate was 91.7% in patients in whom initial ECG rhythm was VF, whereas it was 50% in those in whom initial ECG rhythm was asystole (P=0.275). Between patients with and without ECMO, the rate of admission alive to the hospital (with ECMO, 90% vs without ECMO, 50%) and the ROSC rate (with ECMO, 90% vs without ECMO, 75%) did not differ in the present study.

Discussion

The major finding of the present multicenter registry study is that the ROSC rate and the rate of admission alive to the hospital in out-of-hospital VF patients treated with NIF was high, 86% and 79%, respectively.

NIF for Out-of-Hospital Cardiac Arrest

According to the Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care,[12] intravenous amiodarone should be considered for VF or pulseless VT patients after 3 unsuccessful direct counter-shocks. However, amiodarone was not commercially available until June, 2007 in Japan. Therefore, as alternative for amiodarone, the present study was designed to investigate the feasibility of NIF as a life-saving therapy to defibrillation for victims of out-of-hospital cardiac arrest.

NIF has several advantageous characteristics particularly for emergency care. First, NIF is easily soluble and applicable to secure golden time for resuscitation. Second, its half life is relatively short (T1/2β, 1.53±0.23 h),[5] achieving rapid action and clearance. Third, NIF has only a small cardiac depressant effect and might improve the defibrillation threshold. Fourth, an extracardiac adverse event is not usual.

We previously reported that the intravenous administration of NIF was useful in the emergency treatment of inhibiting drug-refractory VT/VF in high-risk patients, including those with extensive anterior acute myocardial infarction and those who had been already treated with oral amiodarone, oral sotalol, and/or implantable cardioverter defbrillator.[6] However, there have been few single center studies regarding the effect of NIF on patients with shock-resistant, out-of-hospital VF. The rate of admission alive to the hospital was 67% (37 survivors of 55 patients treated with NIF),[15] which was comparable with the present results, where the data were collected from 4 established emergency departments. However, over 20 min spent until NIF was administered following the first shock. When considering the characteristics unique of NIF that decreases the defibrillation threshold,[10] the earlier NIF can be used in the course of cardiac arrest, the greater is the likelihood of at least acute survival.

While proarrhythmic properties of amiodarone are relatively minor as demonstrated in the previous studies,[16] proarrhythmic TdP is the major adverse effect of NIF.[6,17] However, as reported in the previous single center study, the occurrence of TdP was 5% (1 of 21 patients treated with NIF),[18] as low as the present result. The previous study demonstrated that the sensitivity of IKr channels could be modified by its genetic polymorphism or surroundings such as catecholamine, potassium, and pH.[19]

In the present study, the median usage dose of NIF was 25 mg. If a patient's body weight is 60–70 kg, the standard ini-

tial dose should be ~20 mg, 0.3 mg/kg body weight. **Figure 3** shows the simulation of the pharmacokinetics of NIF when the bolus administration at 0.3 mg/kg body weight was performed in a minute in healthy subjects (unpublished data). In this compartment model, the blood concentration of NIF appears to be comparable with that following the standard administration at 0.3 mg/kg body weight/5 min. Although the blood concentration could peak within 10 min in this simulation, it often took 10 to 30 min to recover spontaneous circulation in the present collapsed patients with limited cardiac output by closed chest massage.[20]

Study Limitations

Several limitations of the present study should be mentioned. First, the small number of patients precludes any firm conclusion in this setting designed as a pilot study. Further larger clinical studies with a blinded, randomized design are required. However, resuscitation for out-of-hospital cardiac arrest patients is always critical and is a race against time. It is therefore difficult to explain the study design and its process (eg, blindness and randomization) to potential trial participants. Second, the prognosis after the admission, especially the survival to hospital discharge, was not presented. Third, since intended as a pilot study of various critically ill patients, the present data did not include type of disease, cardiac function (after ROSC or coronary intervention, or under percutaneous ECMO support), serum K^+ and pH concentrations. Fourth, in the recent intensive strategy of the emergency medicine,[21–24] it seems to be hard to distinguish the pharmacological effect of NIF from the mechanical effect of percutaneous ECMO (with the adjunctive therapeutic hypothermia) on CPR.

Conclusions

The present findings indicate that intravenous administration of NIF seems to be feasible as a potential life-saving therapy for advanced cardiac life-support in patients with out-of-hospital VF and therefore further study is warranted.

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Conflict of Interest

None.

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Report From the Japanese Registry of CPR for In-Hospital Cardiac Arrest (J-RCPR)

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