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Evaluation of out-of-hospital cardiopulmonary resuscitation with resuscitative drugs: a prospective comparative study in Japan☆

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Abstract

Objective: This study aimed at evaluating two emergency medical service systems, one in which emergency life-saving technicians (ELSTs) are allowed to administer epinephrine (adrenaline) to patients with out-of-hospital cardiac arrest and one in which ELSTs are allowed to administer epinephrine, lidocaine, and atropine.

Methods: A modified, prospective community health trial was conducted from April 1 to October 31, 2003. Areas served by physician-manned ambulances, where out-of-hospital cardiopulmonary resuscitation (CPR) was performed with resuscitative drugs (experimental areas), were compared to areas served by ELST-manned ambulances, where resuscitative drugs were not administered outside the hospital (reference areas). The sequence of emergency procedures performed in the experimental areas was divided into three phases. Phase I included administration of epinephrine, which simulated administration of epinephrine by ELSTs. Phase II started with the use of lidocaine or atropine. Phases I and II simulated administration of epinephrine, lidocaine, and atropine by ELSTs. Phase III began with administration of another drug. Outcomes, resuscitation rates and 1-month survival rates were determined, and differences between the two types of areas were analyzed.

Results: For non-traumatic cardiac arrest, outcomes through phase II in the experimental areas were significantly better than those in the reference areas. Phase I—only outcomes in the experimental areas were better, but not significantly better, than those in the reference areas.

Conclusion: Use of resuscitative drugs for non-traumatic prehospital CPR appears to be effective in terms of resuscitation rates and 1-month survival rates.

Keywords: Cardiac arrest; Out-of-hospital CPR; Emergency medical services; Epinephrine; Lidocaine; Atropine

1. Introduction

The sequence of events in emergency cardiac care known as the "chain of survival" is essential to improving overall survival from out-of-hospital cardiac arrest [1,2]. However, although the positive effect of early access, early cardiopul-

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monary resuscitation (CPR), and early defibrillation is known [3–6], the effect of early drug administration is still controversial. Whereas epinephrine (adrenaline) is recommended as treatment for cardiac arrest by the American Heart Association [1] and the European Resuscitation Council [7], little has been reported on its effect on survival [8–12].

The National Committee on the "Guidelines of Prehospital Emergency Care by Emergency Life-Saving Technicians (ELSTs)" organized by the Ministry of Health, Labor, and Welfare of Japan and the Fire and Disaster Management Agency, Ministry of General Affairs of Japan, since 2002 have discussed expanding the procedures that ELSTs can perform. ELSTs have served in the field of prehospital emergency care since 1991. They are trained in early CPR and must pass a national examination. They have been allowed to cannulate an intravenous line, to insert an esophageal obturator airway or a laryngeal mask airway, and to defibrillate [13]. They have not been allowed to intubate tracheally or administer drugs. In 2002, the committee granted approval for ELSTs to perform tracheal intubation during out-of-hospital CPR under on-line medical direction from an emergency medicine physician. Another issue discussed was whether ELSTs should be allowed to administer resuscitative drugs for out-of-hospital CPR. Three options were discussed by the committee: (1) that ELSTs administer only epinephrine; (2) that ELSTs administer epinephrine, lidocaine, and atropine; and (3) that ELSTs should not administer any resuscitative drugs because of a lack of sufficient evidence that such drugs have a positive effect on survival from out-of-hospital cardiac arrest.

The present study was carried out to provide information for discussion about whether resuscitative drugs should be introduced into the prehospital emergency medical services (EMS) system in Japan, where ELSTs play an important role. The study aimed at evaluating two target EMS systems: a system in which ELSTs would be allowed to administer epinephrine (target drug) to patients with out-of-hospital cardiac arrest (target system-1) and a system in which ELSTs would be allowed to administer epinephrine, lidocaine, and atropine (target drugs) to patients with out-of-hospital cardiac arrest (target system-2).

2. Materials and methods

2.1. EMS organization

In Japan, local governments organize EMS as a public service. Anyone can use an ambulance free of charge by making a phone call to '119'. Most local governments use a one-tiered system, with basic life support (BLS) ambulances staffed by ELSTs. Before ELSTs were introduced into the Japanese EMS system in 1991, emergency medical technicians (EMTs), who can perform only basic life support procedures such as external chest compressions and ventilation with a self inflating bag and face mask, played the main role in the field of prehospital emergency care. However, the EMTs, were placed as quick transporters for patients suffering an emergency event rather than as medical staff for prehospital EMS [13,14]. ELSTs, who are trained to treat patients with cardiac arrest, are bound to perform basic CPR, insert the esophageal obturator airway or the laryngeal mask airway, perform defibrillation, and then transport patients speedily to the appropriate medical facilities. This means that the principle of the Japanese EMS system for cardiac arrest has shifted somewhat from the "early transport of patients to a medical facility" to the "early restoration of patients' spontaneous circulation".

Several regions, in addition, organize their own two-tiered system: BLS ambulances and physician-staffed ambulances (doctor-manned ambulances). Physician-staffed ambulances provide for prehospital emergency advanced cardiac life support, including administration of the necessary drugs. The doctor-manned ambulance system targets early restoration of spontaneous circulation, which naturally sacrifices early transport of patients to hospitals.

2.2. Conceptual framework and study design

In our need to determine which out-of-hospital services provided to cardiac arrest patients are most critical, we were obliged to compare data obtained from areas served by ELST-manned ambulances with data obtained from areas served by doctor-manned ambulances. This is because it was not ethically possible for us to perform a randomized-controlled trial, nor was it possible for us to change the directives of any of the ELSTs. Neither did we attempt to evaluate the resuscitative drugs themselves. This is because it would have been very difficult to evaluate the effects of the drugs used apart from the effects of other resuscitative measures taken. Instead, by comparing data obtained from areas served by ELST-manned ambulances with data obtained from areas served by doctor-manned ambulances, we were able to evaluate a system in which out-of- hospital CPR is performed without resuscitative drugs with a system in which out-of-hospital CPR is performed with resuscitative drugs. Instead of comparing the effects of the drugs themselves, we assessed the outcomes just after administration of the target drugs. That is, if spontaneous circulation returned with a drug used after the target drug was used, the target drug was regarded as ineffective. It was assumed, then, that there were no other resuscitation options when the target drug was used, as shown in Fig. 1. The ELST-manned system is the standard Japanese EMS system and for purposes of the study is termed the reference system. The doctor-manned system is for purposes of the study termed the experimental system.

Under this conceptual framework, we adopted a modified community health trial to include witnessed cardiac arrests occurring outside the hospital. The study was carried out prospectively from April 1 to October 31, 2003. Ambulance crews were required to complete a written form reporting the patient's age and sex, cause of cardiac arrest, whether it was

	Prehospital measures	*Hospital measures*
Reference system (standard Japanese system)	●Basic CPR ●Cannulation of intravenous line ●Insertion of EOA or LM ●Defibrillation	Everything needed to resuscitate
Experimental system (doctor-manned ambulance system)	Everything needed to resuscitate	Everything needed to resuscitate
Target system-1	●Basic CPR ●Cannulation of intravenous line ●Tracheal intubation ●Defibrillation **+ Use of epinephrine (adrenaline)**	Everything needed to resuscitate
Target system-2	●Basic CPR ●Cannulation of intravenous line ●Tracheal intubation ●Defibrillation **+ Use of epinephrine (adrenaline)** **+ Use of lidocaine** **+ Use of atropine**	Everything needed to resuscitate
Phase I in the experimental area (for evaluation of target system-1)	●Basic CPR ●Cannulation of intravenous line ●Tracheal intubation ●Defibrillation **+ Use of epinephrine (adrenaline)**	Assumed nothing used to resuscitate
Phase I & II in the experimental area (for evaluation of target system-2)	●Basic CPR ●Cannulation of intravenous line ●Tracheal intubation ●Defibrillation **+ Use of epinephrine (adrenaline)** **+ Use of lidocaine** **+ Use of atropine**	Assumed nothing used to resuscitate

Fig. 1. Prehospital and hospital resuscitation measures. CPR, cardiopulmonary resuscitation; EOA, esophageal obturator airway; LM, laryngeal mask airway.

a witnessed or unwitnessed event, and details of resuscitative efforts for each out-of-hospital cardiac arrest.

2.3. Experimental areas and reference areas

Four areas served by doctor-manned ambulances were selected as experimental areas. Two of them are located in the Kanto region (area neighboring Tokyo), and the other two are in the Kansai region (area neighboring Osaka). Four other areas, two from the Kanto region and two from the Kansai region and corresponding to the experimental areas in terms of population size, area, and proportion of the population aged 65 years and older, were selected as reference areas. The reference areas operate a one-tiered system, with ELST-staffed BLS ambulances. Characteristics of the eight areas are summarized in Table 1.

2.4. Sample size

To detect a difference in outcome between cardiac arrest patients treated in experimental areas (experimental group) and such patients treated in reference areas (reference group), sample size was based on resuscitation rates in Japan [5] and was estimated by means of the following formula:

$$n = \frac{\{0.5a + b\sqrt{(\phi/(1+\phi))(1-(\phi/(1+\phi)))}\}^2}{\{(\phi/(1+\phi)) - 0.5\}^2\{(1-p_1)p_2 + (1-p_2)p_1\}}$$

where a was set at 5% significance level (=1.96), b was set at 80% (=1.28) as the statistical power, ϕ was assumed to be 2.5 as the expected odds ratio, p_1 was assumed to be 0.2 as the expected resuscitation rate of the reference group, and p_2 was assumed to be 0.35 as the expected resuscitation rate of the experimental group. Accordingly, a sample size of about 128 was needed for each group to detect a difference in resuscitation rates.

2.5. Action trees

To remove personal bias from the resuscitative procedures, physicians' actions were standardized. The behavior of physicians was not restricted or controlled substantially, but they were requested to administer epinephrine first and then give lidocaine and/or atropine. The sequence of emergency care was expressed as an "action tree", the concept of which derives from decision tree analysis [15,16] and the event tree

Table 1
Characteristics of the experimental and reference areas

	Area size (km^2)	Population (×1000)	Proportion of people aged 65 years and older (%)
Experimental areas			
Funabashi city	85	550	12.6
Cities of Suita, Toyonaka, Minoo	119	860	13.8
Chuwa regional area	166	248	16.0
Wards of Bunkyo and Taito	21	332	19.4
Reference areas			
Sagamihara City	90	605	11.1
Cities of Sakai and Takaishi	148	854	14.9
Konan regional area	206	284	12.0
Sinagawa ward	23	317	17.2

Experimental areas have a two-tiered system combining basic life support (BLS) ambulances and doctor-manned ambulances. Reference areas use the standard Japanese emergency medical services system, a one-tiered system with BLS ambulances.

technique proposed by Dowie et al. [17]. The action tree is shown in Fig. 2; the circular nodes denote chance happenings subsequent to events. In this tree, after basic CPR, the electrocardiogram is monitored, and the heart rhythm is classified as ventricular fibrillation or ventricular tachycardia, pulseless electrical activity, asystole, or the return of spontaneous circulation. Action boxes along the branches show subsequent options that physicians have. For example, defib-

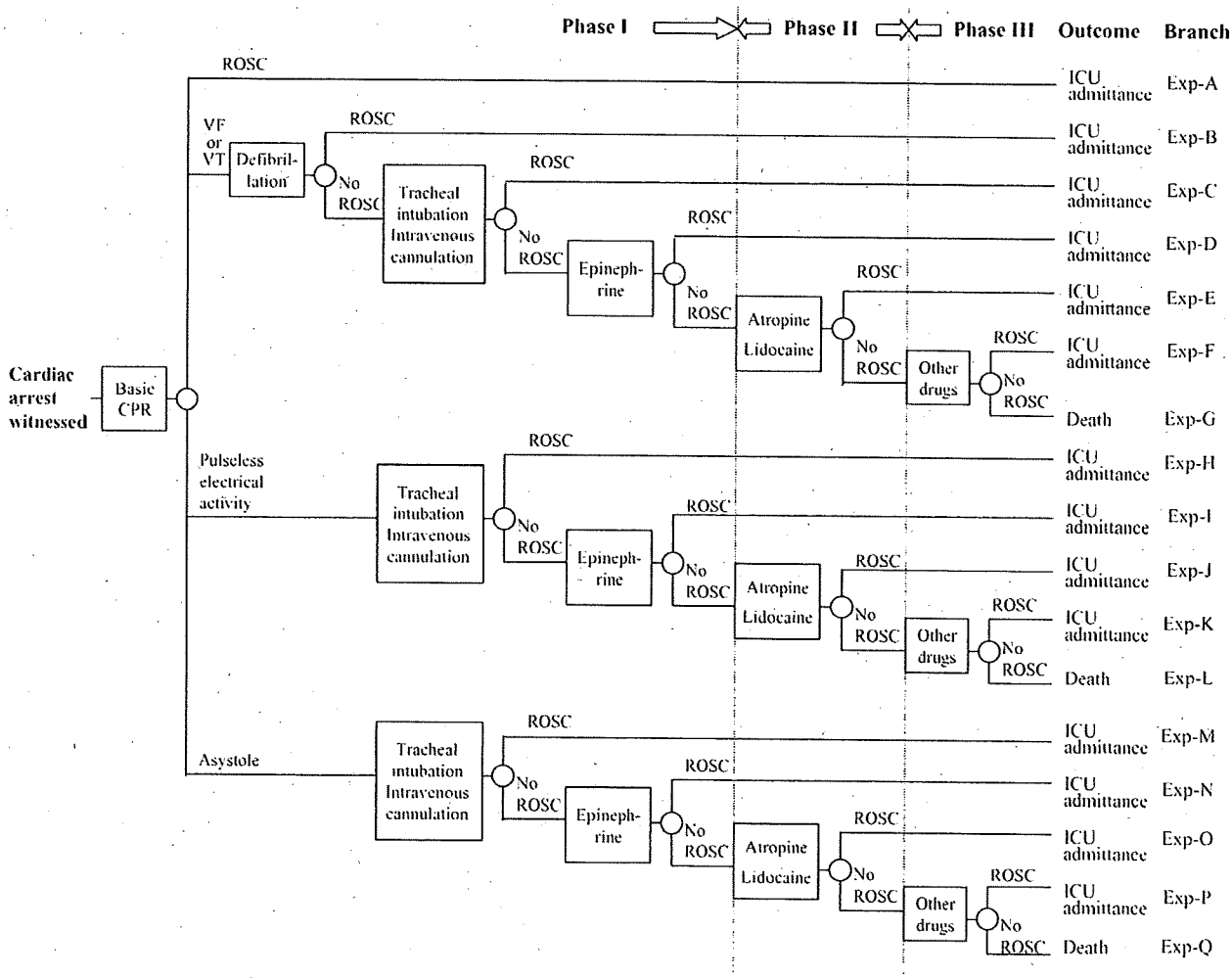

Fig. 2. Action tree of physicians in doctor-manned ambulances. CPR, cardiopulmonary resuscitation; VF, ventricular fibrillation; VT, ventricular tachycardia; ROSC, return of spontaneous circulation; ICU, intensive care unit.

rillation can be done if necessary after epinephrine is administered. Branches from Exp-A to Exp-Q in Fig. 2 show the outcomes, i.e., admittance to the intensive care unit (ICU) or death. Even when the return of spontaneous circulation is observed in the process of resuscitative care, patients are not always admitted to the ICU. Sometimes they die.

The sequence of events was divided into three phases. Phase I included administration of epinephrine. Phase II started with the use of lidocaine or atropine and ended just before the administration of a drug other than one of these three drugs. Phase III began with administration of this other drug and continued until the start of emergency care at the hospital. As shown in Fig. 1, the outcome of phase I was used to evaluate target system-1, out-of-hospital CPR with epinephrine. The outcome of phase II was used to evaluate target system-2, out-of-hospital CPR with epinephrine, lidocaine, and atropine.

The action tree for ELSTs is shown in Fig. 3. This tree was constructed to obtain data on outcomes in accordance with the sequence of events rather than to control the actions of ELSTs.

2.6. Statistical analyses

Difference in mean age between the experimental group and the reference group was analyzed by unpaired *t*-test. Dichotomous data such as sex and cause of cardiac arrest were analyzed by χ^2-test. The time periods from the emergency call to arrival at the scene, from the emergency call to hospital arrival, and from the emergency call to the first defibrillation in cases in which it was performed were compared between the doctor-manned ambulances and BLS ambulances and analyzed by unpaired *t*-test. The outcomes used to evaluate the systems were the percentage of patients with spontaneous circulation admitted to the ICU or an appropriate ward (resuscitation rate) and survival rate 1 month later. Differences in the resuscitation rate and the 1-month survival rate between the experimental group and the reference group were analyzed by χ^2-test. Outcomes through phase II in the experimental group and phase I in the experimental group were compared with the corresponding outcomes of the reference group; these comparisons were by χ^2-test. All tests were two-tailed. *P* values of less than 0.05 were taken as statistically significant.

2.7. Ethics

Data obtained from the study were handled anonymously. The study protocol was approved by the appropriate institutional review board for ethical issues at each participating facility. The study design was approved by the Ministry of Health, Labor, and Welfare of Japan and the Fire and Disaster Management Agency of the Ministry of General Affairs of Japan.

3. Results

Characteristics of the experimental group and reference group are shown in Table 2. There was no statistically signif-

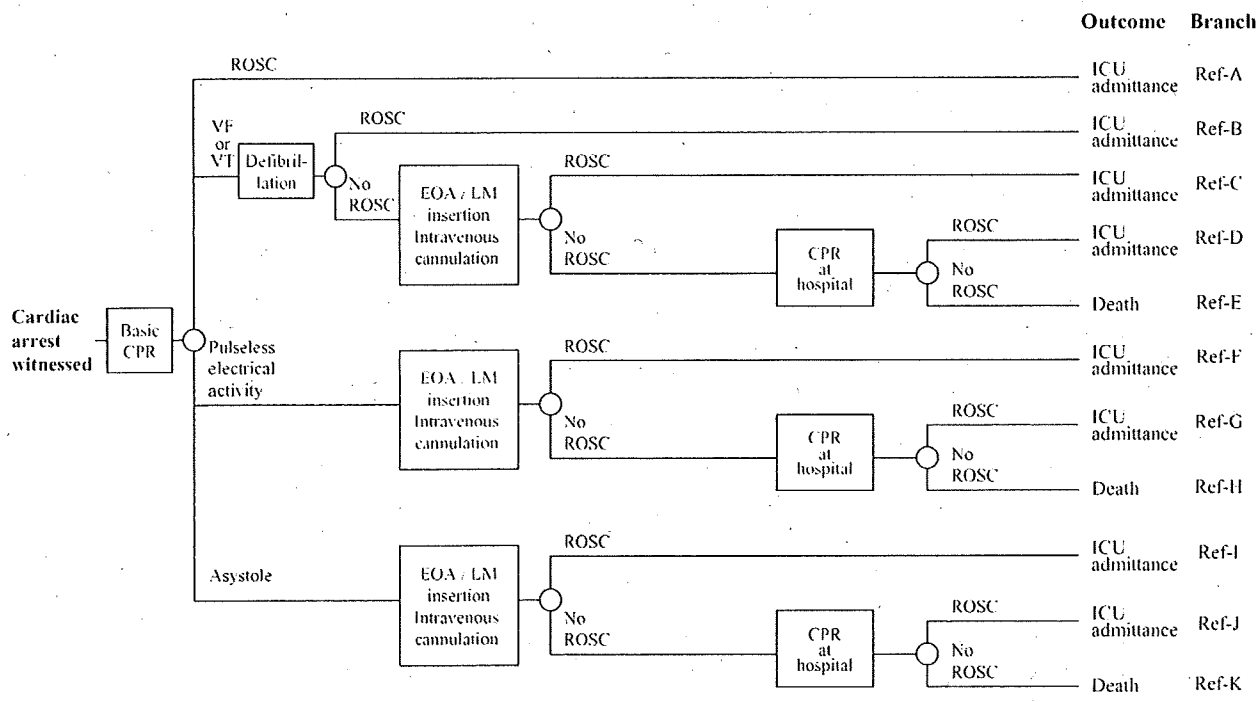

Fig. 3. Action tree of emergency life-saving technicians (ELSTs). CPR, cardiopulmonary resuscitation; VF, ventricular fibrillation; VT, ventricular tachycardia; ROSC, return of spontaneous circulation; EOA, esophageal obturator airway; LM, laryngeal mask airway; ICU, intensive care unit.

Table 2
Characteristics of the two study groups

	Experimental group (doctor-manned ambulances) $n=162$	Reference group (basic life support ambulances) $n=272$	P-value
Age of patients (years)[a]	67.3 (17.5)	69.4 (18.9)	0.275 (t-test)
Sex			
Male	100 (61.7%)	169 (62.1%)	
Female	62 (38.3%)	103 (37.9%)	0.933 (χ^2-test)
Cause of cardiac arrest			
Non-traumatic	120 (74.1%)	222 (81.6%)	
Traumatic	41 (25.3%)	44 (16.2%)	0.025 (χ^2-test)[b]
Unknown	1 (0.6%)	6 (2.2%)	
Time from call to scene arrival (min)[a]	14.1 (6.3)	6.2 (2.7)	<0.001 (t-test)
Time from call to first defibrillation (min)[a]	9.4 (6.7)	10.7 (4.5)	0.360 (t-test)
Time from call to hospital arrival (min)[a]	46.4 (13.6)	28.4 (8.7)	<0.001 (t-test)

[a] Mean (standard deviation).
[b] Excluding unknown causes.

icant difference in age or sex between the two groups. The proportion of cardiac arrests caused by traumatic events in the experimental group was significantly larger than that in the reference group (25.3 and 16.2%, respectively, $P=0.025$). A significant difference was not observed between the two groups in non-traumatic cardiac arrests of cardiac or non-cardiac origin. The proportion of patients in the experimental group who received CPR from a bystander was smaller than that in the reference group (23.5 and 31.3%, respectively), but the difference was not significant ($P=0.081$).

The time from the emergency call to arrival at the scene was significantly shorter for the BLS ambulances (mean: 6.2 min, standard deviation: 2.7) than for the doctor-manned ambulances (mean: 14.1 min, standard deviation: 6.3). However, the start of CPR in the experimental group was not later than that in the reference group because, in the experimental group, BLS ambulance crews of the two-tiered system started basic CPR. If the monitored electrocardiogram showed ventricular fibrillation or ventricular tachycardia, defibrillation was performed. The mean time from the emergency call to the first defibrillation did not differ statistically between the two groups (9.4 and 10.7 min, respectively, $P=0.360$); in the experimental group, the first defibrillation was performed mainly by BLS ambulance crews. Defibrillation was performed one to six times per patient during the out-of-hospital CPR in the reference group (mean: 2.5 times). In the experimental group, defibrillation was performed one to six times per patient (mean: 2.2 times) during phase I and given if needed in phases II and III. The mean time from the emergency call to the time of hospital arrival of the doctor-manned ambulances was 18 min longer than that of the BLS ambulances (Table 2). There was no difference in the mean time from the emergency call to hospital arrival between traumatic arrests and non-traumatic arrest in the experimental group (45.7 and 46.5 min, respectively, $P=0.812$) or the reference group (27.1 and 28.6 min, respectively, $P=0.286$).

Immediate outcomes, i.e., resuscitated patients admitted to an ICU, are shown in Table 3. In cases of cardiac arrest without a traumatic event, the proportion of patients admitted to an ICU was significantly larger in the experimental group than in the reference group (40.8 and 24.4%, respectively, $P=0.001$). Conversely, in cases of cardiac arrest with a traumatic event, the proportion of patients admitted to an ICU was smaller in the experimental group than in the reference group (26.8 and 31.8%, respectively), but the difference was not statistically significant ($P=0.614$).

For cardiac arrest without a traumatic event, the immediate outcomes are shown according to the action trees in Table 4. The proportion of survivors 1 month later was significantly larger in the experimental group (10.8%) than in the reference group (4.5%) ($P=0.027$). The phase I and phase II outcomes in the experimental group were significantly better than those in the reference group (ICU admittance rate and 1-month survival rate, odds ratios = 1.815 and 2.551, respectively, $P<0.05$) (Table 5). The phase I outcome of the experimental group was better, but not statistically better, than that of the reference group (ICU admittance rate and

Table 3
Immediate outcomes in the two study groups

	Experimental group	Reference group
Non-traumatic cardiac arrest		
Admittance to ICU	49 (40.8)	52 (24.4)
Death	71 (51.2)	169 (76.1)
Unknown	0 (0.0)	1 (0.5)
Odds ratio: 2.243 (95% CI: 1.39–3.62; $P=0.001$)[a]		
Traumatic cardiac arrest		
Admittance to ICU	11 (26.8)	14 (31.8)
Death	30 (73.2)	30 (68.2)
Unknown	0 (0.0)	0 (0.0)
Odds ratio: 0.786 (95% CI: 0.31–2.01; $P=0.614$)		

The values in parenthesis are given in percentage.
[a] Excluding unknown outcomes. ICU, intensive care unit; CI, confidence interval.

Table 4
Immediate outcomes and number of non-traumatic cardiac arrest patients surviving at 1 month according to the action tree branches in the two study groups

Branch	Immediate outcome	Phase of return of spontaneous circulation	Number of cases (percentage of total)	1-Monsth survival (percentage of total)
Experimental group (n=120)				
Exp-A	ICU admittance	I	0 (0.0)	0 (0.0)
Exp-B	ICU admittance	I	6 (5.0)	5 (5.0)
Exp-C	ICU admittance	I	4 (3.3)	4 (3.3)
Exp-D	ICU admittance	I	6 (5.0)	0 (0.0)
Exp-E	ICU admittance	II	4 (3.3)	1 (0.8)
Exp-F	ICU admittance	III	0 (0.0)	0 (0.0)
Exp-G	Death		16 (13.3)	
Exp-H	ICU admittance	I	2 (1.7)	0 (0.0)
Exp-I	ICU admittance	I	9 (7.5)	1 (0.8)
Exp-J	ICU admittance	II	3 (2.5)	0 (0.0)
Exp-K	ICU admittance	III	1 (0.8)	0 (0.0)
Exp-L	Death		23 (19.2)	
Exp-M	ICU admittance	I	1 (0.8)	1 (0.8)
Exp-N	ICU admittance	I	5 (4.2)	1 (0.8)
Exp-O	ICU admittance	II	3 (2.5)	0 (0.0)
Exp-P	ICU admittance	III	5 (4.2)	0 (0.0)
Exp-Q	Death		32 (2.7)	
Reference group (n=222)				
Ref-A	ICU admittance		4 (1.8)	2 (0.9)
Ref-B	ICU admittance		6 (2.7)	2 (0.9)
Ref-C	ICU admittance		2 (0.9)	1 (0.5)
Ref-D	ICU admittance		10 (4.5)	1 (0.5)
Ref-E	Death		26 (11.7)	
Ref-F	ICU admittance		0 (0.0)	0 (0.0)
Ref-G	ICU admittance		15 (6.8)	1 (0.5)
Ref-H	Death		41 (18.5)	
Ref-I	ICU admittance		1 (0.5)	1 (0.5)
Ref-J	ICU admittance		14 (6.3)	2 (0.9)
Ref-K	Death		102 (45.9)	

ICU, intensive care unit.

Table 5
Outcomes of non-traumatic cardiac arrest patients of the reference group and experimental group

		Odds ratio	P-value
Percentage of ICU admittance (number of patients)			
Phases I and II in experimental group (n=120)	35.8 (43)	1.815 (95% CI: 1.12–2.95)	0.016
Phase I in experimental group (n=120)	27.5 (33)	1.233 (95% CI: 0.74–2.05)	0.418
Reference group (n=222)	24.3 (52)	1	
Percentage of 1-month survival (number of patients)			
Phases I and II in experimental group (n=120)	10.8 (13)	2.551 (95% CI: 1.08–6.01)	0.027
Phase I in experimental group (n=120)	10.0 (12)	2.333 (95% CI: 0.98–5.57)	0.051
Reference group (n=222)	4.5 (10)	1	

ICU, intensive care unit; CI, confidence interval.

1-month survival rate, odds ratios = 1.233 and 2.333, respectively, $P > 0.05$) (Table 5).

4. Discussion

4.1. Non-traumatic cardiac arrest

Our study results showed overall that the prehospital EMS system with doctor-manned ambulances is more effective than the BLS ambulance system for non-traumatic cardiac arrest in terms of resuscitation rate and 1-month survival rate; i.e., early advanced cardiac life support is advantageous for resuscitation from non-traumatic cardiac arrest. Study patients treated by physicians in doctor-manned ambulances received advanced life support 14 min earlier on average than patients treated by BLS ambulance crews and not given resuscitative drugs until after arrival at the hospital. Doctor-manned ambulances are in use in many European countries [2,18,19], whereas in the United States, paramedics provide advanced cardiac life support for prehospital cardiac arrest patients because doctor-manned ambulances there are con-

sidered an inefficient use of physician resources [2]. In Japan, it would be difficult to extend the doctor-manned ambulance system to the whole country because of the limited number of physicians committed to emergency medicine. Expanding procedures that ELSTs can perform is an alternative to nationwide introduction of doctor-manned ambulances.

The sequence of events initiated by physicians staffing the doctor-manned ambulance was divided into three phases. From the start of the event to the end of phase II is a simulation of target system-2, i.e., the EMS system in which ELSTs would administer epinephrine, lidocaine, and atropine. Outcomes of CPR from the start of the event until phase II were better than those of the reference group in terms of resuscitation and 1-month survival rates. Thus, target system-2 is likely to be more effective than the reference system. Phase I is a simulation of target system-1, i.e., the EMS system in which ELSTs would administer epinephrine only. The phase I outcomes were better than those in the reference group, but statistical significance was not achieved. This does not necessarily mean that target system-1 is not effective because the outcomes improved gradually as the phase advanced. The results imply that target system-1 is more beneficial than the present standard Japanese system.

Another important result of the study was that the proportion of patients resuscitated before drug administration in the experimental group (branches Exp-A, -B, -C, -H, and -M in Fig. 2) was larger than the proportion in the reference group (branches Ref-A, -B, -C, -F, and -I in Fig. 3), although statistical significance was not achieved (proportions of resuscitated patients were 10.8 and 5.9%, respectively, $P > 0.05$). Not only early drug administration but also the behavioral principle of physicians, attaching importance to early restoration of spontaneous circulation rather than early transport, might benefit prehospital CPR.

The present findings indicate that the preferable plan is to adopt a doctor-manned ambulance system nationwide. If this is difficult to do because of a shortage of physicians, the second best option is likely the target system-2, i.e., that ELSTs administer epinephrine, lidocaine, and atropine. The third best option would be target system-1, i.e., that ELSTs administer epinephrine only. Which system should be adopted will be determined on the basis of several factors: cost of training ELSTs, methods of on-line medical control, and risk of accidents. Additionally, how much the behavioral principles should be shifted is also an important and difficult issue. The reason why doctor-manned ambulances delayed transport of patients was that physicians performed as many resuscitative procedures as possible upon arrival at the scene, including intubation, intravenous cannulation, defibrillation, drug administration, and other procedures they thought necessary. When weight is given to early restoration of spontaneous circulation, inevitably early transport of the patients is sacrificed [20] because there is a trade-off relation between them. Although policymakers must be interested in the optimum balance between the two, the present study did not clarify what that balance should be.

4.2. Traumatic cardiac arrest

In contrast to the outcome of CPR for non-traumatic cardiac arrest patients, the resuscitation rate for patients with traumatic arrest was better in the reference areas was than in the experimental areas, although the difference was not statistically significant. The results may be explained simply by the small sample size. The numbers of cases, 41 and 44, are too small for reliable results. It is also possible that the higher proportion of serious cases in the experimental group introduced a bias into the study results. Third, sacrificing early transport of patients to the hospital might have caused the negative outcome. This third possibility should be considered carefully when the behavioral principle of the ELSTs is being evaluated.

4.3. Study design

Little has been reported on the positive effect of resuscitative drugs such as epinephrine. Direct comparison between survival rates and administration of such drugs occasionally yields misleading results. If, for instance, drugs tend to be used more for persons who are difficult to resuscitate than for persons who are easily resuscitated, drugs can appear to influence survival negatively. To the contrary, if drugs tend not to be used when the probability of resuscitation is poor, the positive effect of drug use is likely overestimated. There is an inherent selection bias when drugs are used with medical judgment. To avoid this selection bias, it is most preferable to perform a randomized-controlled trial in which drugs are administered randomly to patients suffering cardiac arrest. Randomized-controlled trials, however, are extremely difficult to perform on ethical grounds. The second-most preferable approach is a community intervention study in which two different community groups, i.e., areas where ELSTs use drugs en route to the hospital and areas where they do not, are compared for rates of survival from cardiac arrest. However, this was not possible under Japanese law. In addition, for ethical reasons, we could not restrict the prehospital use of other drugs, although use of other drugs masks the real effect of target drugs. Under these restricted circumstances, we abandoned evaluation of the effect of drugs. Instead, we evaluated prehospital EMS systems in which drugs are administered.

The action tree constructed for physicians was medically reasonable. The procedures conducted by emergency physicians were not restricted or controlled; only their action steps were determined.

4.4. Study limitations

The number of patients treated in this study differed between the experimental areas and the reference areas, although the areas were matched in terms of regional characteristics. It is likely that doctor-manned ambulances did not respond to all cardiac arrests in the experimental

areas. Selection bias, however, was unlikely to have occurred for witnessed non-traumatic cardiac arrests.

This comparative study involved two different classes of emergency personnel, physicians and ELSTs. The results of the study, therefore, must be interpreted carefully. If a decision is made that ELSTs should be allowed to administer resuscitative drugs during prehospital EMS, the results of the program should be evaluated because several factors could have distorted the outcomes of this study. Resuscitation techniques of ELSTs could be inferior to those of physicians. This could have caused overvaluation of the target systems. In contrast, this study intrinsically undervalued the target systems by reason of the study design, as shown in Fig. 1. The effect of early drug use could have been underestimated in this study because ELSTs can arrive at the scene as much as 8 min sooner than physicians [21].

5. Conclusion

Early administration of resuscitative drugs in out-of-hospital CPR for witnessed non-traumatic cardiac arrest seemed to be effective in terms of resuscitation rate and 1-month survival rate. This effectiveness was observed when epinephrine, lidocaine, and atropine were administered. Even the system under which ELSTs administered only epinephrine seemed to be more beneficial than the present Japanese EMS system, which prohibits ELSTs from administrating resuscitative drugs. The present findings support a recommendation that ELSTs be allowed to administer resuscitative drugs during prehospital EMS.

Conflict of interest

There are no conflicts of interest.

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