Prognosis in Hypoxic Ischemic Encephalopathy

Supachai Paiboonpol, MD*

**Division of Neurology, Department of Medicine, Ratchaburi Hospital, Ratchaburi*

A retrospective review of survivors of cardiopulmonary arrest included 56 patients. Twenty two had a good outcome and thirty four were seriously impaired. Depth and duration of post arrest coma correlated significantly with poor neurologic outcome. Seventy percent of the seriously impaired patients never regained consciousness and non emerged from coma within five days; all of the patients with good outcome were alert within twenty hours after resuscitation. Coma, motor unresponsiveness, absent brainstem reflexes were closely associated with dismal prognosis for neurologic outcome. This study cannot provide a basis for discontinuation of life support at any specific time.

Keywords: *Prognosis, Hypoxic ischemic encephalopathy, Cardiac arrest, Cardiopulmonary resuscitation*

J Med Assoc Thai 2005; 88(7): 903-8
Full text. e-Journal: *http://www.medassocthai.org/journal*

In the twenty first century the cardiopulmonary resuscitation technique has improved survival and functional status after cardiopulmonary arrest due to hypoxia, myocardial infarction, cardiac arrhythmia, myocarditis or other conditions[1,2]. Many studies have demonstrated the value of artificially supporting circulation for several minutes until cardioactive drugs or electrical stimulus re-institute cardiac function and output[3,4]. Reports dealing with survival after cardiopulmonary resuscitation have largely failed to evaluate the quality of survival from the neurologic status[5-7], although some studies considered the predictive value of neurologic examination after cardiac arrest and successful cardiopulmonary resuscitation[6-14].

Patients who survive cardiopulmonary arrest fall into two categories; they are alert, or else they are comatose. The comatose survivor of cardiopulmonary resuscitation posses difficult ethical decisions regarding life-care measures when prognosis for survival and final outcome of neurologic status are uncertain. The present study conducted a retrospective study, case record form, of survivors from cardiopulmonary arrest to provide preliminary data relating to these questions.

Correspondence to : Paiboonpol S, Division of Neurology, Department of Medicine, Ratchaburi Hospital, Ratchaburi 70000, Thailand. Phone: 0-1981-2035, 0-3231-5884, 0-3232-2916, 0-3232-7999, E-mail: supacpai@ccme.or.th

Material and Method

The present study reviewed the medical records form of patients 14 years of age or older who sustained cardiopulmonary arrest, and were admitted to Ratchaburi Hospital, Bangkok, Thailand from January 1, 2000 to December 31, 2003. Cardiopulmonary arrest was defined as loss of consciousness due to cardiac arrhythmia or asystole, documented by an electrocardiogram, associated with apnea, and requiring standard methods of cardiopulmonary resuscitation. Hypoxic injury was isolated from other possible cause of prolonged unconsciousness by excluding patients with major metabolic encephalopathy or drug toxicity.To exclude acute or chronic structural brain disease by neurological examination and CT scan of the brain. To exclude irreversible cardiac damage as the cause of death after initially successful cardiopulmonary resuscitation. Patients who survived at least 24 hours were selected. Fifty-six patients satisfied these criteria.

From reviewing follow-up data of these patients it became apparent that they fell into two groups: a functional group (group 1) with either normal intellect or sufficient ability to care for themselves in a supervised setting. The other group (group 2) was neurologically impaired, with either severe dementia or persistent comatose vegetative state and total dependence on nursing personal care.

Pre-arrest risk factors and intellectual status could not be assessed because of incomplete

information. Medical records were reviewed to detected the use of sedatives, narcotics, and major tranquilizers. Seizures were diagnosed depending on physician and nursing progress notes.

Examination of the comatose patient was based on the methods of Plum and Posner[16]; comments on respiratory status, reflex movements, oculocephalic responses, and response to voice or pain were usually entered in the chart. Many survivors were followed up after discharge.

All patients in group 2 were followed until death. Of the 22 patients in group 1, three died during initial hospitalization, four were lost to follow up after discharge, and 15 were followed for 12-36 months after discharge.

Descriptive statistics were used to analyze the clinical data to compare the groups with respect to initial level of consciousness, highest level of consciousness obtained, coma duration, and seizure activity. Because of repeated testing on the same data, the p values are not to be interpreted literally. The p values were perceived as a means of ranking the variables by level of importance.

Results

There was no significant difference between the groups regarding sex, location of arrest and diagnosis of the cause of the arrest (Table 1).

Ventricular fibrillation was the most common pre-arrest arrhythmia, followed by ventricular tachycardia and asystole. Following resuscitation, normal sinus rhythm was more commonly seen in the group 1, but this difference was not statistically significant (Table 2).

Following cardiopulmonary resuscitation, 18.2 percent in group 1 had spontaneous respiration

Table 1. Patient characteristics

Patient	group 1 (n = 22)	group 2 (n = 34)	p-value
Male	12 (54.5)	20 (29.4)	0.100
Female	10 (45.5)	14 (41.2)	
Mean aged	62.7	60.5	
Aged ranged	47-76	45-72	
Location of arrest			
Out of hospital	3 (13.6)	8 (23.5)	0.671
In hospital	8 (36.4)	14 (41.2)	
ICU with monitoring	3 (13.6)	4 (11.8)	
CCU with monitoring	8 (36.4)	8 (23.5)	
Diagnosis			
Acute myocardial infarction	14 (63.6)	22 (64.7)	0.186
Arrhythmia	8 (36.4)	8 (23.5)	
Myocarditis	0 (0)	4 (11.8)	

Table 2. Arrhythmia

Pre-arrest rhythm	group 1	group2	p-value
Ventricullar fibrillation	12 (54.5)	22 (64.7)	0.795
Asystole	5 (18.2)	4 (14.7)	
Ventricular tachycardia	5 (22.7)	8 (23.5)	
Post-arrest rhythm			
SVT	5 (22.7)	9 (26.5)	0.583
Normal sinus rhythm	14 (63.6)	17 (50.0)	
Atrial fibrillation	3 (13.6)	6 (17.6)	
Third degree AV Block	0 (0)	2 (5.9)	

and 68.2 percent were triggering the respirator (Table 3), while 79.4 percent of patients in group 2 failed to breathe spontaneously ($p < 0.05$).

Of the patients in group 1, twenty (90.9 percent) were arousable or awake immediately after cardio-pulmonary resuscitation (Table 4), while only one patient in group 1 (4.5 percent) was arousable to pain. This difference was statistically significant ($p < 0.05$). One patient in group 2 (2.9 percent) made non reflex movements to pain and was in a deep coma, no response to pain following cardiopulmonary resuscitation, whereas twenty four (70.6 percent) patients were in deep coma after resuscitation. In all, 95.5 percent of patients in group 1 had more than reflex motor response to painful stimulation when first examined. All patients who were deeply comatose and without spontaneous respiration immediately after cardiopulmonary resuscitation fell in group 2.

Duration of coma was timed from the end of cardiopulmonary resuscitation, and termination of coma was defined as the point at which the patient responded to voice (level 2 in Table 4). There was a steady decline in the number of patients recovering from coma to normal mental status as the duration of coma increased (Table 5). There was a significant difference between the groups concerning the duration of coma ($p < 0.002$). Half of group 1 had an essentially normal mental status examination by the time of hospital discharge. In group 2, 70.6 percent of the patients never became responsive at all prior to death. The median value for highest level of responsiveness attained was 1 for group 1, in contrast to 6.0 for group 2 (definitions in Table 4), a statistically significant difference ($p < 0.001$).

In terms of ultimate survival, all patients not in coma after resuscitation and 75 percent of those comatose less than 24 hours survived to discharge from hospital. Fifty percent of patients initially in a coma survived to discharge. Coma alone was a negative prognostic factor.

Of the fourteen group 2 patients (41.2 percent) who had seizures, these persisted for at least 12 hours after arrest (Table 6). Five patients (22.5 percent) in group 1 had seizure activity; in each case, this ceased within 6 hours after arrest and did not recur during a prolonged period of outpatient follow-up.

Brainstem reflexes included pupillary light reaction and oculocephalic maneuvers were recorded on most patients at the time of initial evaluation (Table 7). In group 2, eight patients had both response initially, and in sixteen both were absent. In group 1, fifteen patients had both response initially, and in two, both were absent. All cases in which responses were absent in the first evaluation after cardiopulmonary resuscitation had poor outcomes.

Of the entire group of patients, seizure activity after discharge was seen in only two severely demented group 2 patients. One of these was the only patient in the present series who was discharged on maintenance anticonvulsants. Seizure activity in both cases was limited;one patient experienced two isolated generalized seizures 3 months after cardiac arrest,

Table 3. Initial respiratory status

Initial respiratory status	group 1	group 2	p-value
Spontaneous respiration	4 (18.2)	0 (0)	0.0001
Patient on respirator, triggering	15 (68.2)	7 (20.6)	
Patient on respirator, not triggering	3 (13.6)	27 (79.4)	

Table 4. Initial level of consciousness

Level	Description	group 1	group 2	p-value
0	Normal	1 (4.5)	0 (0)	0.0001
1	Confused but alert	8 (36.4)	0 (0)	
2	Drowsy, confused but responds to voice	9 (40)	0 (0)	
3	Responds to deep pain	2 (9.0)	1 (2.9)	
4	Non reflex movement to pain	1 (4.5)	1 (2.9)	
5	Decorticate or decerebrate posturing	1 (4.5)	8 (23.5)	
6	Comatose,no response to pain	0 (0)	24 (70.6)	

Table 5. Coma duration

Duration	group 1	group 2	p-value
<1 hour	3 (13.6)	0 (0)	0.0001
1-8 hour	5 (22.7)	0 (0)	
8-16 hour	9 (40.9)	0 (0)	
16-24 hour	5 (22.7)	4 (11.8)	
24-48 hour	0 (0)	6 (17.6)	
Until death	0 (0)	24 (70.6)	

Table 6. Seizure activity

Seizure activity	group 1	group 2	p-value
No seizure activity	17 (77.3)	20 (58.8)	0.552
Focal seizure	1 (4.5)	2 (5.9)	
Generalized seizure	2 (9.0)	6 (17.6)	
Myoclonic seizure	2 (9.0)	6 (17.6)	

Table 7. Brainstem reflexes on initial evaluation

Pupillary light reflex	group 1	group 2	p-value
Present	20 (90.9)	18 (52.9)	0.0029
Absent	2 (9.1)	16 (47.1)	
Doll's eye			
Present	15 (68.2)	8 (23.5)	0.0001
Absent	2 (9.1)	19 (55.9)	
Not recorded	5 (22.7)	7 (20.6)	
Both present	15 (68.2)	8 (23.5)	0.0015
Both absent	2 (9.1)	16 (47.1)	

and the other had a terminal episode of status epilepticus.

Ultimate survival was strikingly different for the two groups. Only two patients in group 2 survived hospitalization; both were severely demented. One died of pneumonia in a nursing home 6 months after discharge and the other died in status epilepticus 19 months after discharge. Of the patients characterized as functional, two died of recurrent arrhythmia during the same hospital admission and 20 survived to be discharged. Of the survivors, 14 are living at home independent in activities of daily living. Two of these patients were lost to follow-up 3 months after discharge. One patient is living at home, described as mildly confused, and has the residuals of a dominant parietal lobe syndrome, but after 1 year discharge he is independent in activities of daily living. Four patients remain in nursing homes; two were said to be mentally normal but incapacitated by cardiac disease; two others were intermittently confused and needed supervision for personal needs, but could feed and dress themselves.

Discussion

During the past few decades tremendous technological advances in resuscitation medicine have occurred. Despite such advances as early initiation of cardiopulmonary resuscitation by bystanders and the use of advanced cardiac life support in both prehospital and in-hospital settings, the survival rates for pre hospital cardiac arrest to hospital discharge are less than 20 percent[17]. As if the high mortality were not dismal enough, more than half the survivors experience significant neurologic deficits. Only 3 to 10 percent of resuscitated patients are finally able to resume their pre-cardiac-arrest lifestyles[18].

The predictive data may be viewed from several perspectives;the clinician needs to know how long life support is reasonable for the apparently badly damaged patient. Although the fixed and severe neurologic deficit that may result from anoxic injury are well-delineated[19], the criterior for predicting the functional outcome of patient surviving cardiopulmonary arrest remain unclear. Bokonjic and Buchthal reviewed 74 patients with either carbon monoxide poisoning or cardiopulmonary arrest and noted the correlation between the duration of post anoxic unconsciousness and recovery of mental function. Most of their recovered patients emerged from coma within 16 hours, and intact survivors were not seen after 48 hours of coma following cardiac arrest or after 20 hours of coma following cardiac arrest or after 20 hours of coma in cases of carbon monoxide poisoning. Their study supports a significant predictive relationship between duration of post anoxic coma and ultimate outcome. But, a clear clinical definition of unconsciousness was not presented, making it difficult to apply the data at the bedside. The present study indicate with good reliability that the majority of patients with a good outcome will emerge from coma within 16 hours, with an outer limit of approximately 24 hours.

Mueller-Jensen, Neunzig and Emskotter had analyzed the oculocephalic response and vestibulo-ocular reflex in 81 patients with coma from various causes show the importance of reflex eye movements for outcome prediction. Compared with oculocephalic response testing, vestibuloocular analysis provided

more evidence and allowed more precise study of ocular motility in comatose patients. The results indicated that in all cases with preserved vestibuloocular reflex (independent of the cause of coma) the assumption of a good outcome is justified and was correct in a maximum of 67 percent. Ninety two percent of the patients with abolished reflex eye movements died. The combination of absent vestibuloocular reflex and abolished pupillary light reaction allows prediction of negative outcome in 100 percent and shows the paramount importance of these two brainstem reflexes[10]. In the present study all cases in which brainstem reflexes were absent in the first evaluation after cardiopulmonary resuscitation had poor outcome.

The transplantation team and researcher need to identify poor outcome patients as early in the clinical course as possible and with complete rejection of positive identifications. This retrospective data is not sufficiently detailed to determine the duration of reflex posturing after arrest. It is clear that patients may not respond to voice for hours after cardiopulmonary resuscitation and still do well. In the present study, the clinical findings that were strongly indicative of poor outcome on first evaluation were absence of all motor responsiveness, absence of respiratory effort, and the absence of brainstem reflexes. Seizures were relatively frequent but the numbers were insufficient to establish any prognostic significance, although seizure activity persisting beyond 4 hours after cardiopulmonary resuscitation seem to herald a poor outcome. There was a striking rarity of late postanoxic epilepsy in patients followed for 1 to 2 years. No patient in group 1 had seizure activity after discharge from hospital in follow-up that averaged 18 months. A number of questions remain to be answered by a prospective study before definite criterior can be established for the prediction of the survival and good neurologic function after cardiopulmonary arrest. The early recognition of patients who may require aggressive therapeutic measures is important, since animal studies indicate that the success of therapeutic intervention to prevent central nervous system damage requires intervention within 20 minutes after cardiopulmonary resuscitation, if not actually during cardiopulmonary resuscitation[20]. It must emphazied that the data presented are preliminary and cannot provide an indication for termination of life support in a specific instance.

The ability to accurately assess patients and develop reliable prognosis is important for three reasons. Arriving at an accurate assessment and realistic prognosis is central to informing families about probable outcome. Provision of information and advice to families concerning the benefits and burden of proposed treatments must be linked with realistic goals of treatment. The ongoing dialogue that must occur between family members and the health care team is most useful when based on a firm foundation of accurate assessment. Finally, the just development of resources within the health care system is assuming increasing importance in today's environment. Limiting resource consumption by patients with little hope of recovery has become increasingly important to prevent the inadvertent denial of resources to patients with better chances of recovery. It has become well recognized that ischemic and post ischemic events can cause significant neurological damage[17-20]. The focus of research today is to further elucidate the pathophysiology of ischemic brain damage and to test strategies to successfully resuscitate the brain.

Acknowledgement

The author wishes to thank all the medical staff in the Department of Medicine for care of these patients and clinical review of the presented paper.

References

1. Bernard S, Buist M, Monteiro O, Smith K. Induced Hypothermia using large volume, ice-cold intravenous fluid in comatose survivors of out-of-hospital cardiac arrest:a preliminary report. Resuscitation 2003; 56: 9-13.
2. Ebell M. Prearrest predictors of survival following in-hospital cardiopulmonary resuscitation: a meta-analysis. J Fam Pract 1992; 34: 551-8.
3. Jordan D. Resuscitation experience within the hospital. JAMA 1964; 188: 181.
4. Lemire JG, Jhonson AL. Is cardiac resuscitation worthwhile? A decade of experience. N Engl J Med 1972; 288: 970-2.
5. Liberthson RR. Pre-hospital ventricular defibrillation. N Engl J Med 1974; 291: 317.
6. Bell JA, Hodgson HJ. Coma after cardiac arrest. Brain 1974; 97: 361.
7. Castagna J, Weil MH, Shubin H. Factors determinating survival in patients with cardiac arrest. Chest 1974; 65: 527-9.
8. Wildsmith JAQ, Dennyson WG, Myers KW. Results of resuscitation following cardiac arrest. Br J Anesth 1972; 44: 716-20.
9. Willoughby JO, Leach BJ. Relation of neurological findings after cardiac arrest to outcome.

Br Med J 1974; 3: 437.
10. Mueller-Jensen A, Neunzig HP, Emskotter T. Outcome prediction in comatose patients: significance of reflex eye movement analysis. J Neurol Neurosurg Psychiatry 1987; 50: 389.
11. Maiese K, Jennings F, Baynes K, Heier L, Volpe BT. Persistent cognitive impairment in cardiac arrest survivors. Ann Neurol 1988; 24: 131.
12. Levy DE, Caronna JJ, Singer BH, Lapinski RH, Frydman H, Plum F. Predicting outcome from hypoxic-ischemic coma. JAMA 1985; 253: 1420.
13. Denton R, Thomas AN. Cardiopulmonary resuscitation: a retrospective review. Anaesthesia 1997; 52: 324-7.
14. Krumholz A, Stern BJ, Weiss HD. Outcome from coma after cardiopulmonary resuscitation: relation to seizure and myoclonus. Neurology 1988; 38: 401-5.
15. Teres D, Brown RB, Lemesshow S. Predicting mortality of intensive care coma. Crit Care Med 1982; 10: 86.
16. Plum F, Posner JB. The diagnosis of stupor and coma. 3rd ed. Philadelphia: FA Davis, 1982.
17. Tisherman SA, Grenvik A, Safar P. Cardiopulmonary-cerebral resuscitation: advanced and prolonged life support with emergency cardiopulmonary bypass. Anaesthesiol Scand 1990; 94: 63-72.
18. White BC, Grossman LI, Krause GS. Brain injury by global ischemia and reperfusion: a theoretical perspective on membrane damage and repair. Neurology 1993; 43: 1656-65.
19. Bokonjic N, Buchtal F. Postanoxic unconsciousness as related to clinical and EEG recovery in stagnant anoxia and carbon monoxide poisoning. In: Meyer JS, Gastraut H, eds. Cerebral anoxia and the electroencephalogram. Illinois: Spring-field, 1961; 118-27.
20. Nemoto EM. Postischemic amelioration of brain damage. In: Hoffman KA, Zulich K, eds. Proceedings of the third kolner symposium on cerebral and coronary vascular disorders and infarcts. New York City: Springer-Verlag New York, Inc., (in press).

การทำนายโรคจากภาวะหัวใจหยุดเต้นหลังการฟื้นคืนชีพในผู้ป่วยสมองขาดเลือดและออกซิเจน

ศุภชัย ไพบูลย์ผล

การทำนายโรคในผู้ป่วยที่รอดชีวิตจากสมองขาดเลือดและออกซิเจนในภาวะหัวใจหยุดเต้นมีผู้ป่วยรอดชีวิตทั้งหมด 56 ราย มี 22 ราย ที่การฟื้นตัวอยู่ในเกณฑ์ปกติ, 34 ราย การฟื้นตัวมีการสูญเสียการทำงานของระบบประสาทอย่างมาก ความลึกและระยะเวลาของการไม่รู้ตัวหลังการฟื้นคืนชีพมีความสัมพันธ์อย่างมีนัยสำคัญทางสถิติกับการสูญเสีย การทำงานของระบบประสาท ร้อยละ 70 ของผู้ป่วยที่มีการสูญเสียการทำงานของระบบประสาทไม่มีการฟื้นตัวของการรับรู้เลยห้าวันหลังการฟื้นคืนชีพ ผู้ป่วยทุกรายที่ไม่สูญเสียการทำงานของระบบประสาท มีการรับรู้หลังการฟื้นคืนชีพภายใน 24 ชั่วโมง การหมดสติ การไม่ตอบสนองต่อสิ่งกระตุ้นของร่างกายและปฏิกิริยาของก้านสมองมีความสัมพันธ์อย่างมีนัยสำคัญทางสถิติกับการฟื้นตัวของระบบประสาท การศึกษานี้ไม่สามารถนำไปอ้างอิงในแง่ของการหยุดการรักษาต่อของผู้ป่วย