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Supplementary

2020 Korean Guidelines for Cardiopulmonary Resuscitation. Part 5. Post-cardiac arrest care

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MAJOR CHANGES IN 2020 POST-CARDIAC ARREST CARE GUIDELINE

The 2020 Korean Post-cardiac Arrest Care Guidelines are medical recommendations derived based on scientific evidence for post-cardiac arrest care. These guidelines are based on the 2020 scientific consensus and treatment recommendations of the International Liaison Committee on Resuscitation and we additionally considered the research papers in the post-cardiac arrest care field which were published after the International Liaison Committee on Resuscitation review.[1,2] In these guidelines, topics which are clinically important and needed further consideration were reviewed in the form of adaptation or hybridization. Meta-analyses or scoping reviews for addi-

tional PICOs (Population, Intervention, Control, Outcomes) were also performed.

The level of evidence (LOE) used the definition of the American Heart Association. It was divided into level A, the highest level, to level C, the lowest level.[3] Details are as follows. Level A is a LOE based on one or more high-quality randomized controlled studies, a meta-analysis of results of high-quality randomized controlled trials (RCTs), or one or more randomized controlled studies from a high-quality registry. Level B-R (randomized) is a LOE based on one or more moderate quality randomized controlled studies or a meta-analysis of results of randomized controlled studies with moderate quality. Level B-NR (non-randomized) is a LOE based on one or more well-performed non-randomized observational studies or moderate quality evidence from a well-performed registry, well-performed randomized observational studies, or meta-analysis results from registry studies. Level C-LD (limited data) is a LOE based on a RCT or a non-random observational study. This level is based on results of studies with limitations in study design and implementation, randomized controlled studies, non-random observational studies, or meta-analysis results of studies with limitations in study design and implementation as registry studies, or physiological or mechanical studies in human. Level C-EO (expert opinion) is based on consensus opinion of experts.

The recommendation grade was judged on the basis of direction (benefit and harm) and strength (strong recommendation and weak recommendation) based on the recommendation in the GRADE (Grading of Recommendations Assessment, Development and Evaluation) method. Classification is divided into three categories used by the American Heart Association.[3,4] Class I is when the benefit of the care or intervention is very high relative to the risk (it is appropriate for most physicians to provide care or intervention to most patients). Class IIa is when a care or intervention is generally useful (with some important exceptions, it is appropriate for most physicians to provide care or intervention). Class IIb is when a care or intervention has a positive effect, although the evidence is not clear. Class III (no benefit) is when care or intervention is ineffective (it is the case when high-level studies have not demonstrated efficacy). Class III (harm) is when a care or intervention has a higher risk than benefits (in case of harm).

Compared to the 2015 guidelines, changes made in the 2020 guidelines are as follows.

Airway and breathing

We recommend avoiding hypoxemia in adults who have a return of spontaneous circulation (ROSC) after a cardiac arrest (Class I, Level C-LD).

We suggest to apply 100% oxygen until oxygen saturation (SpO_2) or partial pressure of oxygen in the arterial blood (PaO_2) can be accurately measured (Class IIa, Level C-LD) in adults who have ROSC after a cardiac arrest. In addition, we suggest avoiding hyperoxemia by titrating the fraction of inspired oxygen to target an oxygen saturation of 92% to 98% in patients who remain comatose after ROSC (Class IIb, Level B-R).

We suggest maintaining a partial pressure of carbon dioxide in the arterial blood ($PaCO_2$) within a normal physiological range of 35 to 45 mmHg in adults who have ROSC after a cardiac arrest (Class IIb, Level C-LD).

Intervention for acute coronary syndrome

We suggest performing coronary angiography after neurological recovery from hospitalization rather than early coronary angiography for adults without ST segment elevation on electrocardiography (ECG) after ROSC when no obvious non-cardiac cause is identified (Class IIb, Level B-NR).

We suggest performing early coronary angiography in the case of electrical instability with persistent ventricular tachycardia or ventricular fibrillation, or cardiogenic shock even if there is no ST segment elevation on the ECG after ROSC (Class IIa, Level B-NR).

Temperature control

We recommend performing targeted temperature management (TTM) to all adult cardiac arrest patients who do not respond to verbal commands after ROSC regardless of the initial ECG rhythm (Class I, Level B-R).

A target temperature of 32°C to 36°C is recommended for adult patients who do not follow commands after ROSC (Class I, Level BR). It is reasonable to maintain TTM for at least 24 hours after achieving target temperature (Class IIa, Level B-NR).

We do not recommend the routine use of rapid infusion of cold fluids intravenously to induce hypothermia after ROSC in a prehospital setting (Class III, Level A).

Control of seizures

We recommend treatment of clinically apparent seizures in comatose adults after ROSC (Class I, Level C-LD). Anticonvulsants that are commonly used for the treatment of seizures caused by other etiologies may be considered for the patients with seizures after ROSC (Class IIb, Level C-LD).

We suggest that routine seizure prophylaxis is not used in comatose adults after ROSC (Class III, Level B-NR).

Use of prophylactic antibiotics

The benefit of the routine use of prophylactic antibiotics in pa-

tients with ROSC is uncertain (Class IIb, Level B-R).

Neuroprognostication in comatose adult patients treated with TTM after ROSC

The neurological prognostication in an adult comatose patient after ROSC should not be performed by only one test result. It should use a multimodal approach using the results of various tests such as clinical examination, electrophysiology, biomarkers, and imaging (Class I, Level B-NR). Even though the individual test is performed earlier, we suggest using the multimodal approach at a minimum of 72 hours after normothermia (5 days after ROSC) (Class IIa, Level B-NR).

Bilateral absent pupillary light reflexes or corneal reflexes, quantitative pupillometry in patients who remain comatose at 72 hours or later after ROSC may predict a poor neurological outcome in combination with other prognostic tests (Class IIb, Level C-LD).

The presence of myoclonus and status myoclonus within 72 hours of ROSC may predict a poor neurological outcome in combination with other prognostic tests (Class IIb, Level B-NR). We suggest electroencephalography (EEG) recording in case of status myoclonus to find related epileptic activity (Class IIb, Level C-LD).

Bilateral absent N20 waves on somatosensory evoked potential (SSEP) more than 24 hours after ROSC may predict a poor neurological outcome in combination with other prognostic tests (Class IIb, Level B-NR).

The presence of unequivocal seizures on EEG during the 72 hours after ROSC may predict a poor neurological outcome in combination with other prognostic tests (Class IIb, Level B-NR).

Burst suppression on EEG after sedation has cleared at 72 hours or more after ROSC may predict a poor neurological outcome in combination with other prognostic tests (Class IIb, Level B-NR).

The absence of a normal trace within 36 hours after ROSC in amplitude-integrated EEG monitoring may predict a poor neurological outcome in combination with other prognostic tests (Class IIb, Level B-NR).

High serum levels of neuron specific enolase (NSE) measured at 24-72 hours after ROSC may predict a poor neurological outcome in combination with other prognostic tests (Class IIb, Level B-NR).

Reduced gray-white matter ratio (GWR) on brain computed tomography (CT) within 24 hours after ROSC, or extensive areas of restricted diffusion and reduced apparent diffusion coefficient (ADC) on magnetic resonance imaging (MRI) at 2 to 7 days after ROSC may predict a poor neurological outcome in combination with other prognostic tests (Class IIb, Level B-NR).

Withdrawal of life-sustaining treatment

We suggest that withdrawal of life-sustaining treatment based on predicted poor neurological outcome are postponed until at least 72 hours after ROSC in adult comatose patients treated with TTM (Class IIa, Level C-LD).

Organ donation

Organ donation should be considered in comatose patients who fulfill neurological criteria for brain death after ROSC or cardiac arrest patients who have not achieved ROSC from cardiac arrest (Class IIb, Level C-LD).

Rehabilitation and long-term care

We recommend structured assessment for anxiety, depression, post-traumatic stress, and fatigue for cardiac arrest survivors (Class I, Level B-NR).

We recommend that cardiac arrest survivors have multimodal rehabilitation assessment and treatment for physical, neurological, cardiopulmonary, and cognitive impairments before hospital discharge and receive a comprehensive, multidisciplinary discharge plan including medical and rehabilitative treatment (Class I, Level C-LD).

Cardiac arrest center

Adult patients with non-traumatic out-of-hospital cardiac arrest (OHCA) should be considered for transport to a hospital that can provide 24-hour coronary angiography and TTM (Class IIb, Level B-NR).

Post-cardiac ARREST CARE

In the 2020 CPR guidelines, post-cardiac arrest care is also emphasized as a key element in the chain of survival. The post-cardiac arrest care algorithm presents treatment strategies and therapeutic goals to be considered in the initial stabilization stage followed by investigation of the cause of cardiac arrest, treatment of reversible causes, and intensive care strategies to reduce additional brain damage. In addition, continued management planning, such as secondary prevention and rehabilitation for cardiac arrest survivors, and neurological prognostication for patients who do not recover consciousness after a certain period of time are newly included (Fig. 1).

Airway and breathing

When a cardiac arrest patient is unconscious after ROSC, the airway should be secured by endotracheal intubation if endotracheal intubation has not been performed during CPR. There is no RCT

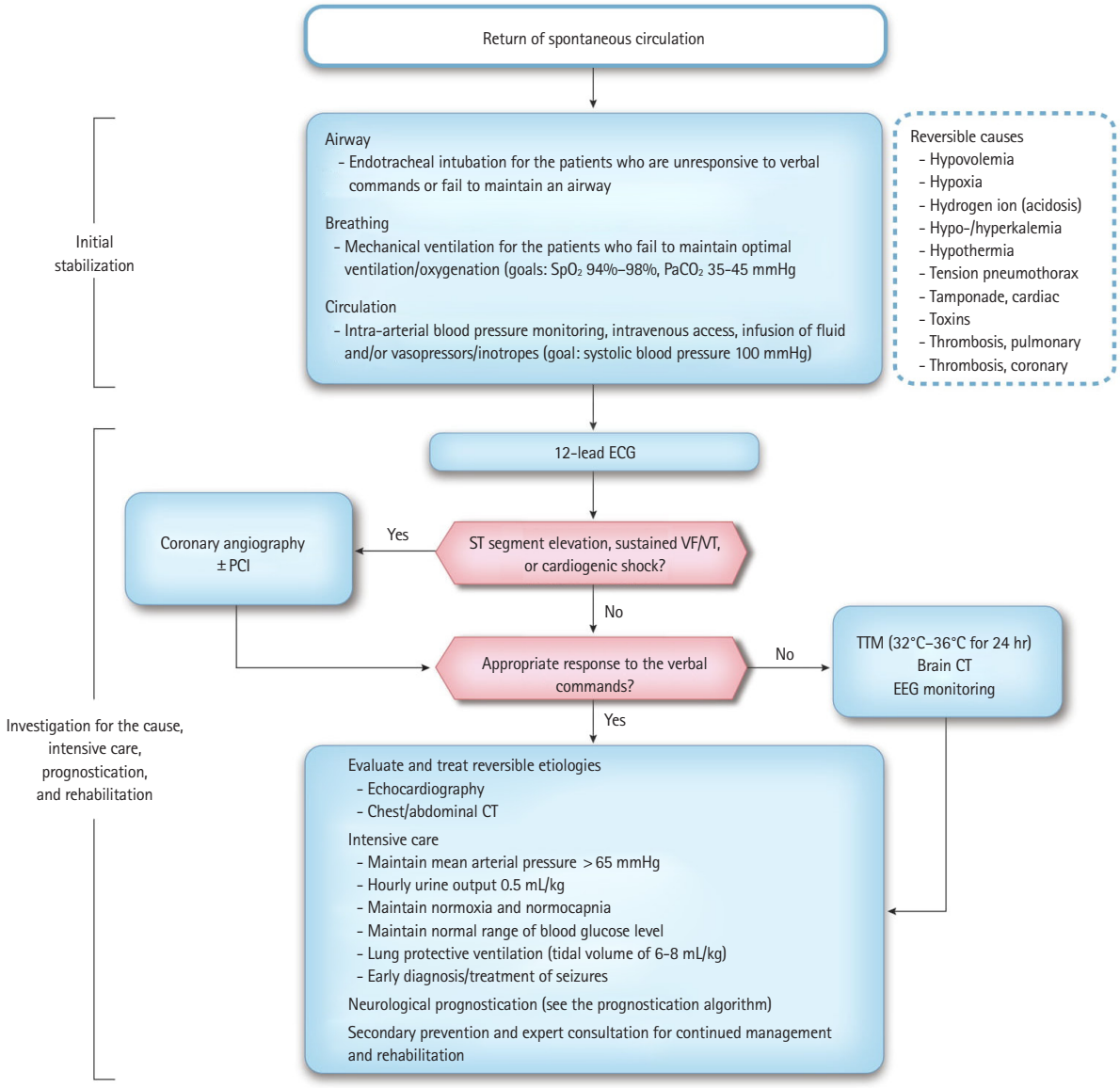

Fig. 1. Algorithm for post-cardiac arrest care. ECG, electrocardiography; PCI, percutaneous coronary intervention; VF/VT, ventricular fibrillation/ventricular tachycardia; TTM, targeted temperature management; CT, computed tomography; EEG, electroencephalography.

determining whether different oxygen concentrations or avoiding hypoxemia before measuring SpO_2 or PaO_2 is associated with clinical outcomes. However, one observational study has reported that hypoxemia is associated with a poor outcome. Hypoxemia is theoretically likely to cause tissue damage by causing tissue hypoxia.[5] Therefore, we recommend avoiding hypoxemia in adults who have ROSC. In addition, to prevent further damage due to tissue hypoxia, we suggest to apply 100% oxygen until SpO_2 or PaO_2 can be accurately measured in adults who have ROSC.

Several RCTs have compared low-dose oxygen treatment with high-dose oxygen treatment in prehospital settings in patients after ROSC.[6-9] While oxygen treatment at a lower concentration compared to 100% oxygen treatment had no benefit for survival discharge in a cluster RCT, targeting of oxygen concentrations lower than 100% showed a benefit for survival discharge.[6-8] In a meta-analysis that evaluated survival discharge with good neurological outcomes, there was no benefit of supplying low concentrations of oxygen.[5,7] In a study comparing the target treatment for normal oxygenation and the target treatment for hyperoxia after the intensive care unit admission, the target treatment for normal oxygenation had no benefit. On the other hand, in subgroup analysis of a RCT, treatment that avoided hyperoxia had benefit for 90-day survival with good neurological outcome.[9-11] Although four observational studies showed that targeted treat-

ment for hyperoxia was associated with low survival rates or poor neurological outcomes, six studies did not show such association.[5,12-20] Therefore, we suggest avoiding hyperoxemia by titrating the fraction of inspired oxygen to target an oxygen saturation of 92% to 98% in patients who remain comatose after ROSC.

Hypercapnia increases cerebral blood flow and intracranial pressure, while hypocapnia reduces cerebral blood flow and intracranial pressure. Two RCTs comparing two different $PaCO_2$ targets have been reported. A RCT with a low LOE compared treatments targeting high-normal $PaCO_2$ (44–46 mmHg) with low-normal $PaCO_2$ (33–35 mmHg) after ROSC and the other RCT with a low LOE compared treatments targeting moderate hypercapnia (50–55 mmHg) with normocapnia (35–45 mmHg). As a result, treatment targeting high hypercapnia did not have benefits compared to treatment targeting normal or low-normal hypocarbia.[11,21] In observational studies, it has been reported that hypercapnia shows contradictory results or it is not associated with good outcome.[5,12,15,22-24] Hypocapnia has also showed similar results and no studies had reported its benefits. Therefore, we suggest maintaining $PaCO_2$ within a normal physiological range of 35–45 mmHg in adults who have ROSC after a cardiac arrest.

Circulation

Hemodynamic stabilization

Immediately after ROSC, arterial pressure should be continuously monitored by rapidly inserting an arterial catheter along with ECG monitoring. If the arterial catheter cannot be inserted, blood pressure should be measured frequently by a non-invasive method until the patient is hemodynamically stabilized.

One observational study has compared a group with a mean arterial pressure (MAP) of 70 to 90 mmHg and a group with a MAP >90 mmHg and found that the group with MAP >90 mmHg had better neurological outcomes.[25] A RCT has compared a MAP of 85 to 100 mmHg target and a MAP of 65 mmHg target and found that cerebral oxygen saturation measured by near-infrared spectroscopy was higher in the group with a MAP of 85 to 100 mmHg without showing differences in neurological outcomes between the two groups.[26] A RCT has compared a MAP of 80 to 100 mmHg target with a 65 to 75 mmHg target and found no difference in NSE or neurological outcomes at 48 hours.[27] However, in both RCTs, the sample size was insufficient to determine the effect on survival or neurological outcomes. Thus, it is currently difficult to determine the effect of a treatment targeting an average MAP >65 mmHg

Hypotension can reduce oxygen delivery to tissues by decreasing perfusion to organs including the brain. Hypotension after ROSC (defined as systolic blood pressure <90 mmHg or MAP <65 mmHg) is associated with death and poor neurological outcomes in a number of observational studies.[28-34] However, the evidence is insufficient to determine a specific hemodynamic goal for post-cardiac arrest patients. It is suggested that hypotension should be corrected quickly, and a hemodynamic goal should be determined for individual patients, while maintaining a systolic blood pressure >100 mmHg.

Investigation for the causes of cardiac arrest and treatment of reversible causes

Intervention for acute coronary syndromes

Acute coronary syndromes are common causes of adult cardiac arrest.[35-37] Thus, 12-lead ECG and cardiac marker tests should be performed as soon as possible after ROSC to confirm the presence or absence of acute coronary syndrome. It is recommended to perform emergency coronary angiography for all cardiac arrest patients with ST segment elevation on ECG after ROSC regardless of their state of consciousness.[38]

In a large-scale RCT conducted in patients with suspected acute coronary syndrome among cardiogenic cardiac arrest patients without ST segment elevation on ECG after ROSC, after comparing the strategy of performing coronary angiography within 2 hours after ROSC and the strategy of performing coronary angiography after neurological recovery, there was no difference in 90-day mortality or neurological outcome.[39] In a meta-analysis of 11 studies (including four RCTs), there was no difference in 30-day mortality rate, neurological outcome, or the ratio of coronary intervention between the strategy of early coronary angiography and the strategy of post-stable coronary angiography.[40] According to results of an additional meta-analysis, in the case of suspected acute coronary syndrome among patients with cardiogenic cardiac arrest and no ST segment elevation on ECG after ROSC, short-term mortality rates were compared between patients who underwent coronary angiography immediately after hospital visit and those who underwent coronary angiography after neurological stabilization. Results revealed no difference in 30-day mortality between the two groups.[36,41-43] In four observational studies comparing short-term mortality of patients who underwent coronary angiography immediately after hospital visit and those who did not undergo coronary angiography, patients who underwent coronary angiography immediately after the hospital visit showed lower mortality than those who did not undergo coronary angiography.[36,43-45] In three observational studies comparing short-term neurological outcome of patients who underwent coronary angiography immediately after admission to the hospital and those who underwent coronary angiography after neurological stabilization, there was no difference in short-term neurological

outcome between the two groups.[36,42,43] In three observational studies, patients who underwent coronary angiography immediately after hospital visit showed a better short-term neurological outcome than those without coronary angiography.[36,43,44] Therefore, we suggest performing coronary angiography after neurological recovery from hospitalization rather than early coronary angiography for adults without ST segment elevation on ECG after ROSC when no obvious non-cardiac cause is identified. Moreover, unlike in the West, it is necessary to take into consideration the reality that there are many sudden cardiac deaths due to coronary artery spasm in Korea. Thus, early coronary angiography should not be routinely performed in patients without ST segment elevation after ROSC when there are no indications for emergenct coronary angiography, including cardiogenic shock, persistent ventricular tachycardia or ventricular fibrillation, and persistent ischemic chest pain.[46] Even if there is no ST segment elevation on ECG after ROSC, when patients are in a state of electrical instability with persistent ventricular tachycardia or ventricular fibrillation, severe coronary artery stenosis has been found in 85% of patients. Moreover, early coronary angiography should be performed even in the case of cardiogenic shock because the possibility of multivascular coronary artery disease and left main coronary artery lesions is high.[37,47,48]

Treatment of pulmonary embolism

There were no RCTs about the treatment of cardiac arrest due to pulmonary embolism. Observational studies evaluating the effectiveness of fibrinolysis treatment in patients with suspected pulmonary embolism have found significant risk of bias with diverse outcomes.[49-53] In two case reports, including 21 patients who underwent CPR or surgical thrombectomy due to cardiac arrest with pulmonary embolism, 30-day survivals were 12.5% and 71.4%, respectively.[54,55] In a case report of patients with cardiac arrest due to pulmonary embolism, 6 out of 7 patients treated with percutaneous thrombectomy showed ROSC.[56] In one RCT and several observational studies, the risk of major bleeding was relatively low in patients who underwent thrombolysis and CPR.[49,51,52]

There is no robust evidence that reperfusion through removal of blood clots in cardiac arrest due to pulmonary embolism can improve the outcomes. However, the risk of death from cardiac arrest is greater than the risk of bleeding from thrombolysis and mechanical or surgical thrombectomy. Therefore, thrombolytic agents, mechanical or surgical thrombectomy can be considered as treatments for cardiac arrest due to pulmonary embolism. Since there are no clear benefits for either technique, the choice of treatment can be determined by the time elapsed from cardiac arrest and the presence or absence of experts.

The effectiveness of thrombolytic therapy in cardiac arrest patients with suspected but unclear pulmonary embolism is currently uncertain. One recent study has reported that the risk of major bleeding in cardiac arrest patients treated with thrombolytics is not high.[51] Therefore, if pulmonary embolism is strongly suspected in the absence of ROSC, thrombolytics can be considered.

Treatment for optimizing neurological recovery

Temperature control

Prevention and treatment of hyperpyrexia

Observational studies have reported that fever is associated with poor outcome in patients who have not received TTM after ROSC.[57-61] Hyperpyrexia occurs in many patients after TTM. However, the association of hyperpyrexia with outcome is not consistent among studies.[62-66] Although the effect of hyperpyrexia on the outcome of post-cardiac arrest patients is not proven, a poor outcome was associated with hyperpyrexia in comatose patients in whom cerebral damage was due to other causes such as cerebral hemorrhage or infarct. The method of preventing or treating hyperthermia is relatively easy to apply.[67,68] Therefore, it is suggested to continuously prevent or treat fever in adult comatose patients after ROSC regardless of whether the patient received TTM.

TTM

- Indication and optimal target temperature

One RCT and a pseudo-randomized trial demonstrated that TTM of 32°C to 34°C can improve neurological outcome at hospital discharge and at 6 months compared to no temperature control in adult OHCA with shockable rhythms. Therefore, OHCA with a shockable rhythm is a main indication for TTM.[69,70]

Three small RCTs have compared TTM at 32°C to 34°C to normothermia in adult OHCA with non-shockable rhythms.[71-73] However, since the sample sizes of the studies were too small and the clinical outcome was not the primary end point, it was difficult to derive meaningful conclusion. A large RCT with moderate LOE (HYPERION trial) including 584 adult OHCA and in-hospital cardiac arrest (IHCA) patients has compared 33°C TTM and 37°C normothermia.[74] The 33°C group showed a significantly better neurologic outcome at 90 days compared to the 37°C group.[74] In the process of evidence review for the 2020 guidelines, results of the HYPERION trial and results of two small-sized randomized controlled studies with very low LOE were included for a meta-analysis. Results revealed that TTM did not reduce the mortality rate at 90 or 180 days compared to normothermia. However, a meta-analysis of two studies that included neurological outcome at 90 or 180 days revealed that 32°C or 33°C TTM reduced the in-

cidence of poor neurological outcomes at 90 or 180 days compared to normothermia.

On the other hand, there is no RCT for IHCA comparing TTM with no temperature control. In a retrospective cohort study with very low LOE involving 1,836 IHCA patients, TTM at 32°C to 34°C was not associated with survival or good neurological outcome compared to those without active temperature control. In a large-scale retrospective cohort study of 26,183 IHCA registry data using propensity scores matched analysis, TTM at 32°C to 34°C was not associated with a good neurological outcome at survival or discharge.[75,76] However, the TTM rate for the patients included in these studies was very low and the risk of bias was high due to a large number of missing data. Therefore, it is difficult to accept that the results of the studies are clinically meaningful and a RCT is necessary.

There are not many RCTs comparing different target temperatures. In a RCT involving 939 OHCA with cardiogenic cause of all rhythms except unwitnessed asystole, TTM at 33°C and 36°C was compared. There was no significant difference between two temperature groups in 6-month mortality, poor neurologic outcome, or side effects. Through these results, ultra-mild hypothermia (36°C) emerged as another target temperature.[77] Meanwhile, in a preliminary RCT comparing TTM of 32°C, 33°C, and 34°C reported in 2018, there was no significant difference in neurologic outcome at 90 days among these groups.[78]

In the 2020 guidelines, we recommend performing TTM to maintain a constant target temperature between 32°C and 36°C to all adult cardiac arrest patients who do not respond to verbal commands after ROSC regardless of the initial ECG rhythm (Class I, Level B-R).

• Timing to initiate and duration of TTM

Several studies have compared the prehospital induction of TTM with hospital induction of TTM. In all seven RCTs with a moderate LOE, there was no significant difference between the groups in mortality or poor neurologic outcome.[79-85]

A meta-analysis of 7 studies also did not show differences in the mortality or poor neurologic outcome at hospital discharge between the two groups.[86] In a study comparing a group of OHCA who were rapidly infused with cold saline during cardiac arrest with a group of OHCA with induced hypothermia after arriving at the hospital, the ROSC rate decreased significantly while acute pulmonary edema increased significantly in patients receiving cold saline infusion during cardiac arrest.[87] In addition, neurologic outcome at 90 days was not different in a study comparing OHCA for whom TTM was rapidly induced by spraying a coolant into the nasal cavity during cardiac arrest with OHCA receiving standard-of-care.[88] There is no evidence yet that starting TTM in the prehospital setting is more beneficial than starting it in a hospital. Therefore, further research is needed.

There is no definitive interventional study that has determined the optimal duration of TTM after cardiac arrest. In a RCT comparing 24-hour with 48-hour TTM for OHCA, neurological outcome at 6 months was not significantly different between the two groups.[89] However, due to a small sample size, the efficacy of 48-hour TTM could not be concluded. Therefore, based on the duration used in two largest aforementioned RCTs, it is reasonable to maintain TTM for at least 24 hours after achieving the target temperature.

• TTM methods

Various cooling methods can be used to induce and maintain a target temperature, but there is no single ideal method yet. External surface cooling methods (e.g., cooling blanket, ice packs, and a wet towel) have been used widely in the past. It has the advantage of being easy to use and convenient to apply. However, it has disadvantages in that the speed of lowering the patient's core temperature is slow. In addition, it is difficult to maintain at a constant level, which adds to the medical staffs' high workload. Recently, cooling equipment using intravascular catheters or external cooling equipment equipped with a precise automatic feedback system have become available. Thus, body temperature control has become easy, but expensive. Therefore, medical staff that plan to perform TTM should consider various factors (e.g., the place to initiate the treatment, staff's ability and experience, speed of induction, stability during maintenance and rewarming, mobility of the equipment, adverse events associated with specific equipment or techniques, convenience of using the equipment, cost, etc.), and the most optimal cooling method should be chosen for individual patients.[90]

The cold crystalloid IV fluid infusion method is relatively easy to use, and it was widely used as a method for inducing hypothermia in prehospital settings or during resuscitation for convenience. However, rapidly infusing a large amount of cold IV fluid during resuscitation or immediately after ROSC is no longer recommended to induce hypothermia because it can significantly increase the incidence of acute pulmonary edema.[79,83,85,86,88]

When performing TTM, the patient's core temperature should be continuously monitored in the esophagus, bladder, or pulmonary artery. The pulmonary artery temperature is the most accurate, but it has a limitation because it requires an invasive procedure. The axillary or oral temperature is not appropriate for measuring change in core temperature, and tympanic temperature probes are difficult to use for a long time and often inaccurate.

The rectal temperature is commonly used, but caution is required because there can be temperature gaps when hypothermia is induced rapidly.[91]

Moreover, there is not enough evidence for an optimal rewarming rate. Therefore, at this point, it is suggested to rewarm at a rate of 0.25°C to 0.5°C per hour, which has been used often in previous studies and maintain normothermia (36.5°C to 37.5°C) up to 72 hours after ROSC in comatose patients even after normothermia is achieved.

Glucose control

In a RCT on patients treated with target blood glucose levels of 72 to 108 mg/dL or 108 or 144 mg/dL, the 30-day mortality rate did not differ between the two groups.[92] In a before-and-after study that used a bundle of care with a target blood glucose level of 90 to 144 mg/dL, the neurological outcome improved after implementing the bundle, but the effect could not be attributed only to the controlled blood glucose level.[93] It may not be appropriate to use blood glucose control methods for critically ill patients based on results of studies on patients with cardiac arrest.[94-96] Although the blood glucose control method in critically ill patients remains controversial, strict control of blood glucose has been associated with an increased incidence of hypoglycemia.[92] Therefore, the target range of 144 to 180 mg/dL is suggested to prevent hypoglycemia, although evidence is still insufficient. Hyperglycemia above 180 mg/dL should be treated with an insulin infusion according to the hospital-specific protocol and care should be taken to prevent hypoglycemia (< 80 mg/dL). If hypoglycemia occurs, it should be immediately corrected by administering a glucose solution.

Control of seizures

In comatose patients after ROSC, the prevalence of seizures, nonconvulsive status epilepticus, and other similar seizures is estimated to be about 20% to 30%.[97] We recommend treatment of clinically apparent seizures to prevent a secondary brain injury in comatose adults after ROSC.[98,99]

If seizures occur or are suspected, EEG should be performed. In addition, considering the high incidence of non-convulsive seizures in comatose patients after ROSC, EEG should be actively performed if possible. There is a debate about whether the EEG method should be continuous EEG in terms of diagnostic utility and cost-effectiveness.[100,101]

However, in comatose patients after ROSC, it is often difficult to clinically confirm whether the patient has seizures due to the use of sedatives or muscle relaxants during TTM. Therefore, it is newly recommended to monitor such patients using continuous EEG.[102,103]

Rapid injections of anticonvulsants are commonly used to control seizures. Fosphenytoin, sodium valproate and levetiracetam are all effective in controlling seizures. However, fosphenytoin is associated with a high incidence of hypotension.[104,105] Sedatives such as propofol and midazolam are also effective in suppressing seizure waves after a cardiac arrest.[106] Continued myoclonic status after ROSC may not respond well to anticonvulsants.[107] We suggest that routine seizure prophylaxis should not be used in comatose adults after ROSC due to the lack of research to support their usage.

Sedation

Sedation therapy to reduce shivering during mechanical ventilation or TTM is a routine treatment after ROSC. However, there is no high-quality evidence to define the duration of sedation and neuromuscular blockade in patients after ROSC. A meta-analysis of sedative drugs used during TTM in 68 intensive care units in various countries has revealed that a wide variety of drugs have been used.[108] Although drugs that might be related to prognosis are currently unknown, it showed that a combination therapy of opioids and sedatives was mainly used. In addition, short-acting drugs such as propofol, dexmedetomidine, and remifentanil provided reliable evaluation of neurological conditions and prognosis. It is recommended to use sedatives with a short duration of action if possible. However, no analysis or treatment policy has been established for the effect of using sedatives after a cardiac arrest. A previous study has suggested that continuous administration of neuromuscular blockers to patients undergoing post-cardiac arrest is associated with a low mortality rate.[109] However, administration of neuromuscular blockers can interfere with neurological examination and make it impossible to detect the occurrence of seizures.

Use of prophylactic antibiotics

Two RCTs and several observational studies on the use of prophylactic antibiotics in post-cardiac arrest care were reviewed.[110-113] In the two RCTs, there were no significant differences in survival, neurological outcome, or infection incidence according to prophylactic antibiotic use.[110,111] In one RCT, the incidence of pneumonia was low in patients receiving prophylactic antibiotics. However, there was no significant difference in survival or neurological outcome between patients receiving prophylactic antibiotics and those who did not receive such antibiotics. Therefore, the benefit of the routine use of prophylactic antibiotics in patients with ROSC is uncertain.[111]

Evaluation of neurological prognostication

Accurate neurological prognostication is important to prevent inappropriate withdrawal of life-sustaining treatment in patients who still have a chance to have potentially meaningful neurological recovery and to avoid futile treatment in patients with a severe and irreversible neurological injury. However, until now, no single test can completely predict prognosis of the comatose patient after ROSC. Thus, it is necessary to integrate the results of multiple tests to prognosticate. In addition, since the process of predicting neurological prognostication may be affected by drugs (sedatives and neuromuscular blockers) and TTM, it should be conducted under conditions that minimize the confounding effects. The 2020 guidelines recommend an approach to perform the neurological prognostication process as follows (Fig. 2). 1) We recommend that neurological prognostication for comatose patients after ROSC should proceed after a sufficient time has elapsed to minimize confounding effects and errors during the recovery period. 2) Even though the individual test may be performed earlier, we suggest using the multimodal approach at a minimum of 72 hours after normothermia (5 days after ROSC). 3) The neurological prognostication in an adult comatose patient after ROSC should not be performed by only one test result. It should use a multimodal approach using the results of various tests such as clinical examination, electrophysiology, biomarkers, and imaging.

Poor neurological outcome could be suspected if at least two findings are observed among the following six test results. If not,

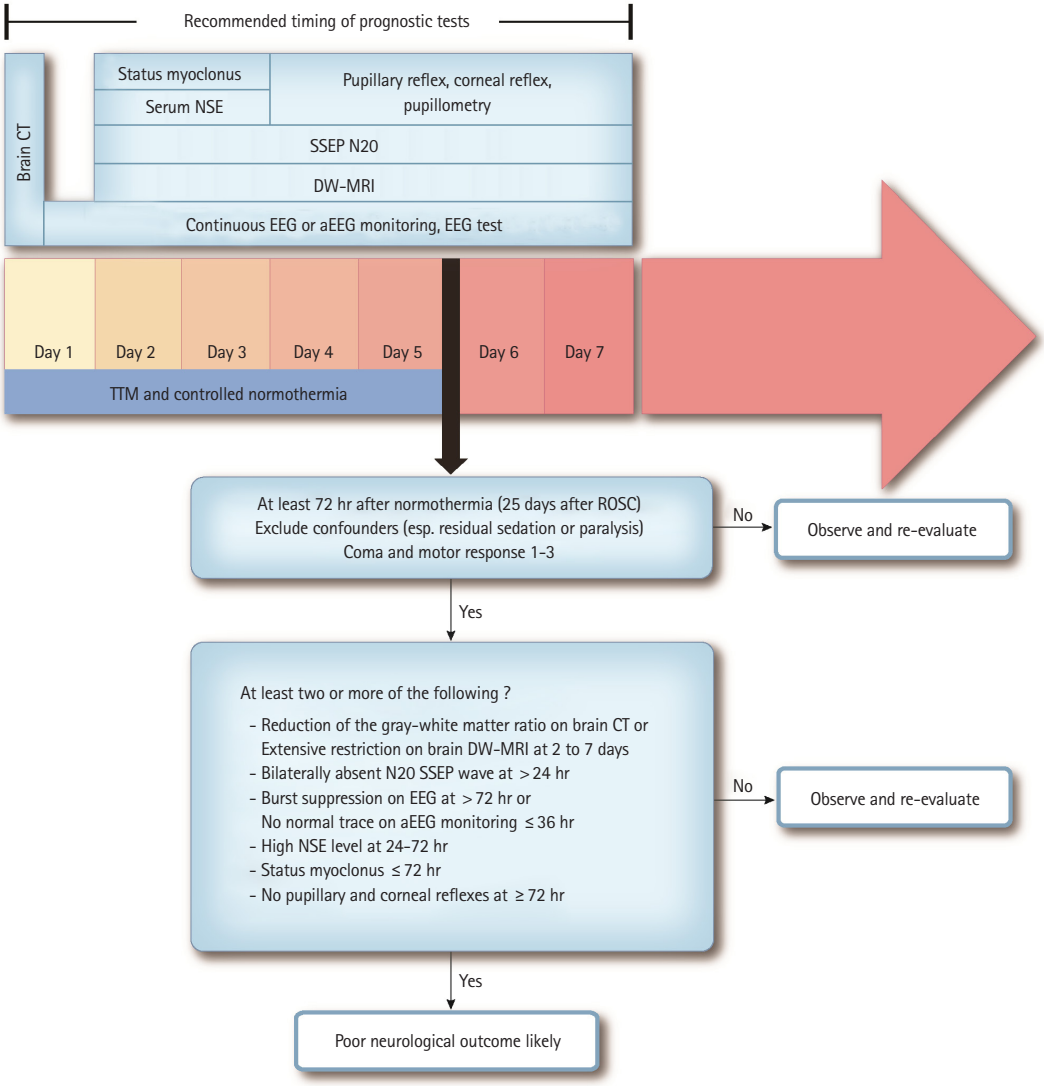

Fig. 2. Algorithm for prognostication after cardiac arrest. CT, computed tomography; NSE, neuron specific enolase; SSEP, somatosensory evoked potential; DW-MRI, diffusion weighted-magnetic resonance imaging; aEEG, amplitude-integrated electroencephalography; EEG, electroencephalography; TTM, targeted temperature management; ROSC, return of spontaneous circulation.

the prognosis should be determined by comprehensively judging various findings after further observation and reevaluation.

1) Reduction of the GWR on brain CT or extensive restriction on brain diffusion-weighted magnetic resonance imaging including ADC at 2 to 7 days; 2) bilaterally absent N20 waves in SSEP test at > 24 hours; 3) burst suppression occurring on EEG at > 72 hours or no normal trace on amplitude-integrated EEG monitoring ≤ 36 hours; 4) high level of serum NSE at 24 to 72 hours; 5) observation of status myoclonus ≤ 72 hours; and 6) loss of both pupillary light and corneal reflexes at ≥ 72 hours.

Clinical examination

Bilateral absent pupillary light reflexes or corneal reflexes, and quantitative pupillometry in patients who remain comatose at 72 hours or later after ROSC may predict a poor neurological outcome in combination with other prognostic tests.[102,114-135] Automated pupillometry provides an objective and quantifiable measurement of the pupillary response. The most common quantitative pupillometry measures, percentage of reduction of pupil size and neurological pupil index, can be used to predict neurological outcome at 72 hours after ROSC.[123,126,136-138]

On the other hand, myoclonus and status myoclonus observed within 72 hours after ROSC may predict a poor neurological outcome. However, it is recommended to evaluate them in combination with other prognostic tests.[102,119,127,129,131,139-143] EEG recordings may also be considered in case of status myoclonus to find related epileptic activity.

Electrophysiology

SSEP

In 21 studies, when bilateral absence of N20 waves was observed in the SSEP conducted at 24 hours or more after ROSC, a poor neurological outcome was predicted with specificity of 50% to 100% and sensitivity of 18.2% to 70.5%.[101,102,114,121,123,127,128,134,144-156] Although decrease in the amplitude of N20 is associated with a poor neurological outcome in some studies, further studies are needed.[152,155,157,158] Since there is a high likelihood that results are affected by confounding factors within 24 hours after ROSC, it is recommended to use bilateral absence of N20 waves more than 24 hours after ROSC in combination with other prognostic tests.

EEG

- Seizures recorded on EEG

In five studies, seizures recorded on EEG within 120 hours after cardiac arrest predicted poor neurological outcome with specificity of 100% and sensitivity of 0.6% to 26.8%.[139,159-162] As seizures recorded on EEG show a low sensitivity for predicting poor neurological outcome, some patients with seizures can recover with a good outcome. Thus, the usefulness of seizures recorded on EEG as a prognostic predictor is currently unclear.

- Burst suppression

In seven studies, burst suppression appearing within 120 hours after ROSC predicted poor neurological outcome with specificity of 90.7% to 100% and sensitivity of 1.1% to 47%.[131,139,144,147,161,163,164] The definition of burst suppression was not consistent for each study and the recording time also varied. In addition, effects of drugs cannot be excluded. Therefore, each study does not show a high LOE. Burst suppression on EEG after sedation has been weaned off at 72 hours or more after ROSC may predict a poor neurological outcome in combination with other prognostic tests.

- Epileptiform discharges

Epileptiform discharges can be divided into two types: rhythmic/periodic discharge and sporadic, non-rhythmic/periodic discharge. In 11 studies, rhythmic/periodic discharges predicted a poor neurological outcome with specificity of 66.7% to 100% and sensitivity of 2.4% to 42.9% if they appeared within 120 hours after ROSC.[102,120,127,151,153,159-161,163,165,166] In 5 studies, sporadic, non-rhythmic/periodic discharges predicted poor neurological outcome with specificity of 66.7% to 100% and sensitivity of 0.4% to 38.5% if they appeared within 120 hours after ROSC.[120,147,151,159,160] The variable definition of epileptiform discharges between studies, the effects of sedative drugs, and the variable background EEG make epileptiform discharges unreliable predictors. Therefore, it is recommended not to use epileptiform discharges as a predictor of poor neurological outcome in comatose patients after ROSC.

- EEG unreactivity

In 15 studies, when EEG unreactivity within 72 hours after ROSC was present, a poor neurological outcome was predicted with specificity of 41.7% to 100% and sensitivity of 50% to 97.1%.[102,119,127,131,145,148,150,160,162,167-172] In addition, stimulation and response were not consistently defined for each study. The effect of drugs was not taken into account either. Thus, it is not recommended to use EEG unreactivity in comatose patients after ROSC as a predictor of poor neurological outcome.

Continuous amplitude-integrated EEG

In comatose patients treated with TTM, the absence of a normal trace within 36 hours after ROSC in amplitude-integrated EEG monitoring may predict a poor neurological outcome in combination with other prognostic tests.[173-175]

Biological marker

In comatose patients treated with TTM, high serum levels of NSE measured at 24 to 72 hours after ROSC may predict a poor neurological outcome in combination with other prognostic tests. However, a cut-off value for predicting a poor neurological outcome with a 0% false-positive rate cannot be clearly recommended.[115,121,124,127,131,135,176-180] It is suggested not to use S-100B protein to predict neurological outcomes in comatose adults after ROSC. It is also suggested not to use serum glial fibrillary acidic protein, serum tau protein, or serum neurofilament protein to predict poor neurological outcomes in comatose adults after ROSC.[181-187]

Neuroimaging

The degree of cerebral edema identified as a reduced GWR on brain CT in comatose patients after ROSC, extensive areas of restricted diffusion in brain MRI, and a reduced ADC can be used to predict poor neurological outcome.

In brain CT, the GWR of a specific area was evaluated (mostly within 24 hours after ROSC) and its specificity for a poor neurological outcome was reported to be 85% to 100%.[116,134,135,176,188-194] However, the specific threshold of the possible GWR and the most appropriate timing of brain CT scan remain unknown.

If diffusion restriction was observed on MRI performed within 5 days after ROSC, the specificity for poor neurological outcome was reported to be 55.7% to 100%.[117,132,134] There have been studies trying to predict poor neurological outcome with ADC values of MRI performed within 7 days after ROSC.[195-197] Quantitative ADC measurements are promising. However, the specific threshold of ADC for predicting poor neurological outcome is unknown due to the availability and diversity of measurement methods.

In comatose patients after ROSC, if used in combination with other predictors, remarkably reduced GWR on brain CT taken within 24 hours after ROSC or extensive areas of restricted diffusion with ADC reduction in brain MRI taken at 2 to 7 days after ROSC is recommended as a predictor.

Withdrawal of life-sustaining treatment

The Well-Dying Act was enforced in February 2018 in Korea. The Act has legally allowed to withdraw life-sustaining care, resulting in a major change in post-cardiac arrest care. Two observational studies with very low LOE showed that early withdrawal of life-sustaining treatment within 72 hours after ROSC was associated with increased mortality or poor neurological function at hospital discharge.[198,199] Therefore, we suggest that withdrawal of life-sustaining treatment based on predicted poor neurologic outcome be postponed until at least 72 hours after ROSC in adult comatose patients treated with TTM.

Organ donation

Transplantation-related studies cannot be conducted prospectively. Therefore, it can be said that results of large retrospective studies have similar impact to those of prospective studies. In addition, complications after transplantation are different in each organ. The quality of donated organs does not depend on whether or not CPR has been performed, but functional warm ischemic time and no perfusion time might play more important roles. After reviewing several retrospective studies, transplantation outcomes of organs donated from donors who died due to failure to achieve ROSC in recent studies were found to be acceptable. It has been reported that transplantation outcomes of donors who died due to brain death after ROSC are not bad compared to those of donors who have not undergone CPR.[200-209] Based on the results of published studies so far, it has been summarized that CPR does not affect outcomes of the transplanted organ.[210] Therefore, organ donation should be considered in comatose patients who]fulfill neurological criteria for brain death after ROSC or cardiac arrest patients who have failed to ROSC from cardiac arrest.

Among patients who have ROSC after CPR, one can be presumed to be brain death if following conditions are met 1) no spontaneous breathing and breathing is maintained with a ventilator; 2) cause of arrest is certain and an irreversible brain injury is proven; 3) absence of more than 5 of 7 brainstem reflexes; and 4) no specific causes of arrest such as carbon monoxide poisoning, metabolic disorders, or suicide attempts which require medical observation. We recommend that medical staff who treat a patient who has suspected brain death should report the suspected brain death for organ donation.[211]

When notifying a suspected brain death after CPR, medical staff should confirm the state of the suspected brain death and the explanation of the suspected brain death notification system to the guardian to confirm the consent for organ donation. Prior to evaluation for organ donation, the degree of awareness of the guardian about the presumed brain death condition and donor family information should be confirmed. Confirmation of donor family information includes confirmation of consent for organ donation, relationship and contact information with the donor, and confirmation of priority guardians.[211]

Rehabilitation and long-term care

Assessment and early rehabilitation after post-cardiac arrest

Cardiac arrest survivors experience a variety of physical, cognitive, and psychological problems, like other critically ill patients.[212] Psychological disorders such as anxiety, depression, and post-trau-

matic stress in particular are experienced by about a third of patients revived from a cardiac arrest. Fatigue is also often accompanied by other disorders.[212-215] Families of cardiac arrest patients also experience severe stress and psychological problems.[216-220] These psychological problems have a significant effect on the long-term prognosis and quality of life of cardiac arrest patients.[216-220] However, there are many cases where adequate treatment cannot be provided because it is not always recognized by the medical staff.[221-223] Therefore, we recommend structured assessment for anxiety, depression, post-traumatic stress, and fatigue for cardiac arrest survivors so that psychological problems that are common to survivors after a cardiac arrest can be identified without missing them and appropriate treatment can be provided to them to improve their long-term prognosis.

Cognitive impairments such as memory, attention, and executive function are commonly observed in cardiac arrest survivors. It is associated with a lower quality of life.[224-229] After intensive care, muscle weakness, gait impairment, dysphagia, and cardiopulmonary impairment are also common.[230] Therefore, we recommend that cardiac arrest survivors have multimodal rehabilitation assessment and treatment for physical, neurological, cardiopulmonary, and cognitive impairments before hospital discharge. Currently, studies on the effects of rehabilitative evaluation and treatment after cardiac arrest are insufficient. However, considering the effects of early rehabilitation for critically ill patients and rehabilitation effects on physical and cognitive impairment in stroke and traumatic brain injury, the effects of rehabilitation interventions after cardiac arrest are also expected and thus further studies are needed.[230-236]

Discharge plan and long-term care after discharge

Various medical problems and disabilities that occur after cardiac arrest can cause difficulties in returning to society and work.[226,237-239] In addition, there is a need for patients and caregivers to provide appropriate information about the patient's condition.[217,240-242] Therefore, comprehensive and multidisciplinary discharge planning, including medical and rehabilitation medical treatment plans, should be established for cardiac arrest survivors.

Three RCTs have demonstrated the effects of long-term care on improvement of long-term outcomes in cardiac arrest survivors. In one study, early, individualized, semi-structured interventions were performed for symptoms of neurological injury to the survivors in the experimental group and a significant improvement in emotional, mental health, and general health items of SF-36 was observed in the experimental group compared to the control group.[243] In the experimental group, overall emotional state and anxiety assessed by the HADS (Hospital Anxiety and Depression Scale) were significantly improved. There was no significant difference in the degree of social participation between the two groups at 1 year. However, the return-to-work rate at 3 months was significantly higher in the experimental group.

In a cost-effectiveness analysis using the same study data, the overall cost did not differ significantly between the group with interventions focusing on early neurological symptoms and the control group. For the incremental cost effectiveness ratio, the intervention was found to be cost-effective.[244] In a RCT of 133 OHCA survivors, relaxation, self-management, and coping strategies were assisted in the experimental group. The psychosocial treatments consisting of cognitive behavioral therapy to reduce depression and anxiety and education on cardiovascular risk factors were provided twice a week for a total of 11 treatments for the experimental group and compared with the conventional treatment group. At 2 years, the risk of cardiovascular death rate was significantly reduced in the experimental group.[245]

In one study, structured information was provided to a randomly assigned experimental group of 168 patients with implantable defibrillators after cardiac arrest or fatal arrhythmia. Phone counseling was conducted once a week (15 to 20 minutes per session) for a total of 8 weeks.[246] Telephone counseling was conducted for the purpose of assisting in the recovery process after implantation of an implantable defibrillator, enhancing self-efficacy, and relieving emotional stress and anxiety. At 6 and 12 months, physical and psychological adaptation, self-efficacy, and medical use were evaluated. As a result, physical concern, anxiety, and fear of death were significantly reduced in the experimental group. Self-efficacy and knowledge of implantable defibrillator management was also significantly improved in the experimental group. In a recent interventional observational study without a control group, a multidisciplinary, structured psychological, cognitive, and medically supported care program that could be provided from hospital discharge to 12 months after discharge was developed and applied for cardiac arrest survivors.[247] The program structure consists of a wide range of cognitive and psychological evaluations during hospitalization, provision of various types of information, telephone consultation on the 2nd day after discharge, multidisciplinary evaluation and consultation for about 1 hour through an outpatient visit at 8, 6, and 12 months after discharge, and so on. The above care treatment program was applied to 19 cardiac arrest survivors. Results confirmed that the quality of life evaluated by SF-36 was improved in almost all areas at 6 months compared to the time of discharge. Therefore, it is recommended to consider the provision of individualized long-term care taking the problems such as cognitive impairment, anxiety, and depression of cardiac arrest survivors into account.

Cardiac arrest center

It is well known that transfer of patients to hospitals where comprehensive post-cardiac arrest care can be performed efficiently after cardiac arrest was associated with survival and good neurological outcomes.[248-264] A meta-analysis of 17 observational studies revealed that patients treated at the cardiac arrest center showed higher survival and neurologically favorable survival discharge rates compared to those treated at the other hospitals. However, there was no significant difference in 30-day mortality or neurological outcomes between the two groups.[265] The reason was that there was no clear definition of cardiac arrest centers and there was no large RCT. In many studies, the availability of 24-hour coronary angiography, TTM, and neurointensive care are included in the definition of a cardiac arrest center. In fact, since ischemic heart disease is the main cause of sudden cardiac arrest, we also suggest that 24-hour coronary angiography and TTM are included in the definition of the centers when defining cardiac arrest centers in Korea.[266]

We suggest that adult patients with non-traumatic OHCA should be considered for transport to a hospital that can provide 24-hour coronary angiography and TTM. It is reasonable to transfer to a cardiac arrest center where coronary angiography is possible. If an OHCA patient visits a hospital where coronary angiography is not possible, it may be effective to immediately transfer the patient to a hospital at a level where coronary angiography is possible. However, considering the domestic reality that only 20% of patients with acute myocardial infarction use emergency medical systems and about half of patients with ST segment elevation acute myocardial infarction visit hospitals where coronary angiography is not possible at the first visit, clear guidelines for transfer of cardiac arrest patients is needed along with a public announcement.[267] In addition, since the concept of a cardiac arrest center has not been established in Korea, it is necessary to discuss the concept of the function, level and designation of cardiac arrest centers in our emergency medical system.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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