

Intensive Care After Resuscitation from Cardiac Arrest: A Focus on Heart and Brain Injury

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Although national statistics are not available, community-wide studies suggest only a minority of patients have return of spontaneous circulation (ROSC) after an out-of-hospital cardiac arrest. Of the estimated 350,000 to 450,000 out-of-hospital cardiac arrests, 100,000 patients have an attempted resuscitation. Of these, 40,000 patients have ROSC and are admitted to ICU. Half of these patients survive the hospitalization and another half of this group survive without major neurologic sequelae. Therefore, less than 3% of all patients who have out-of-hospital cardiac arrests have ROSC, survive the hospitalization, and have a reasonable functional recovery [1]. The fact that many patients who have ROSC ultimately die or fail to have favorable neurologic recovery, suggests that processes that occur after hospitalization, especially in an ICU, have an impact on survival and neurologic recovery. This article addresses the acute care, with emphasis on the cardiac and neurologic aspects, that patients who have postcardiac arrest are provided in the cardiac ICU.

Dr. Geocadin is supported in part by National Institutes of Health (NIH) grants R44-NS-38016 and RO1-HL-EB 71568 and Ms. Hartmann is supported in part by NIH grant R44-NS-38016.

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The factors that influence survival in a prehospital setting are well known, including whether or not the arrest is witnessed and the rapidity in which resuscitative efforts, including defibrillation, are initiated. (See the article by Ornato and Peberdy elsewhere in this issue for discussion of these factors.) Much less is known about the factors that influence survival and neurologic recovery during the first hours and days of ICU evaluation and management of patients who have sudden cardiac death and who have ROSC. In spite of the fact that there has been recent improved short-term survival from out-of-hospital cardiac arrest to hospital admission, the hospital survival rate with favorable neurologic outcomes has been unchanged during the past several years [2].

The lack of national or worldwide guidelines results in marked variability in the management of patients who have sudden cardiac death and ROSC and who are admitted to an ICU. As anticipated, this variability affects outcome. In a study from Sweden [3], a single emergency medical services unit admitted to two hospitals, with similar prehospital care for sudden cardiac death. In this observational series, 579 patients were admitted alive after cardiac arrest to one hospital and 459 patients were admitted alive after cardiac arrest to a second neighboring hospital during a concurrent time interval. Survival was significantly different between the two hospitals. The hospital with improved survival to discharge after ROSC for out-of-hospital cardiac arrest had a more aggressive approach to patient management, including a higher percentage of patients undergoing coronary angiography, echocardiography, electrophysiologic studies, and stress testing. These data suggest that the course of patients who have ROSC after an out-of-hospital cardiac arrest and are admitted to an ICU is affected by the level of care when hospitalized.

Cardiac arrest: etiology and severity

Etiology of cardiac arrest

Autopsy studies show that most sudden death survivors have structural heart disease, with atherosclerotic coronary artery disease by far the most common underlying substrate, seen in approximately 80% of sudden death victims [1,4,5]. In addition to atherosclerotic coronary disease, autopsy evidence of plaque rupture in men and plaque erosion in women who have subsequent coronary thrombosis is the underlying pathology in the majority of cases of sudden cardiac death [6]. Given the frequent prevalence of coronary disease, the majority of patients admitted to the ICU should undergo coronary angiography to define the coronary anatomy with possible revascularization at some point during the hospitalization. The American Heart Association and American College of Cardiology recommend coronary angiography in all survivors of sudden cardiac death [7]. The timing of coronary angiography depends on whether or not there is evidence of acute myocardial infarction or hemodynamic instability and the overall neurologic prognosis.

In patients who do not have evidence of acute ST-segment elevation, myocardial infarction, or cardiogenic shock, delay until a neurologic prognosis is determined seems reasonable.

Other underlying pathologic substrates found in cardiac arrest victims are listed in **Box 1**. These include nonischemic dilated cardiomyopathy; infiltrative cardiomyopathies; primary electrical abnormalities, such as long QT syndrome; presence of drugs that prolong the QT interval; electrolyte abnormalities; and toxins. In addition to cardiac substrates, there are several other causes of sudden death and ventricular arrhythmias. These include pulmonary causes, such as pulmonary embolism, respiratory arrest followed

Box 1. Underlying substrates for out-of-hospital cardiac arrest

1. Coronary artery disease
 - Acute myocardial infarction
 - Chronic ischemic cardiomyopathy
 - Coronary vasospasm or dissection
 - Anomalous coronary artery
2. Nonischemic heart disease
 - Dilated cardiomyopathy
 - Hypertrophic cardiomyopathy
 - Arrhythmogenic right ventricular dysplasia
 - Infiltrative cardiomyopathy
 - Myocarditis
 - Valvular heart disease (aortic stenosis)
3. Primary electrical abnormalities
 - Long QT syndrome
 - Brugada syndrome
 - Wolff-Parkinson-White syndrome
 - Idiopathic ventricular tachycardia
4. Drug or toxin induced
 - Cocaine
 - Proarrhythmia from antiarrhythmic medications
 - QT interval-prolonging drugs, such as erythromycin antibiotics and psychotropic medications
5. Electrolytic or metabolic
 - Thyrotoxicosis
 - Poisoning
 - Hypokalemia, hypomagnesemia
6. Mechanical
 - Pulmonary embolism
 - Tension pneumothorax
 - Trauma

by cardiac arrest from pneumonia, and so forth. In addition to mimicking acute myocardial infarction, primary neurologic events, such as subarachnoid hemorrhage, also can cause neurogenic cardiac injury leading to ventricular fibrillation and cardiac arrest (Fig. 1) [8]. Because subsequent therapy depends to a great degree on the cause of the cardiac arrest, such as heparin for a pulmonary embolism, direct percutaneous coronary intervention for ST-segment elevation myocardial infarction, an evaluation to determine the underlying substrate of sudden cardiac death is important in the early management of these patients.

Cardiac arrest and brain injury

The duration of cardiac arrest as the clinical marker of global ischemia is correlated highly with brain injury [9–12]. The precise duration of cardiac arrest with the cessation of blood flow to the brain represents the primary insult and is one of the most important clinical factors in determining the severity of the brain injury [10,12]. During the Brain Resuscitation Clinical Trials (BRCT), a duration of cardiac arrest of 6 minutes or longer and a resuscitation time to achieve ROSC of 28 minutes or longer indicate poor neurologic recovery. Shorter cardiac arrest times and resuscitation times, indicating lesser injury, are associated with favorable outcomes. A European study reports a similar observation of patients having favorable outcomes with short cardiac arrest times (4.1 minutes) and unfavorable outcomes

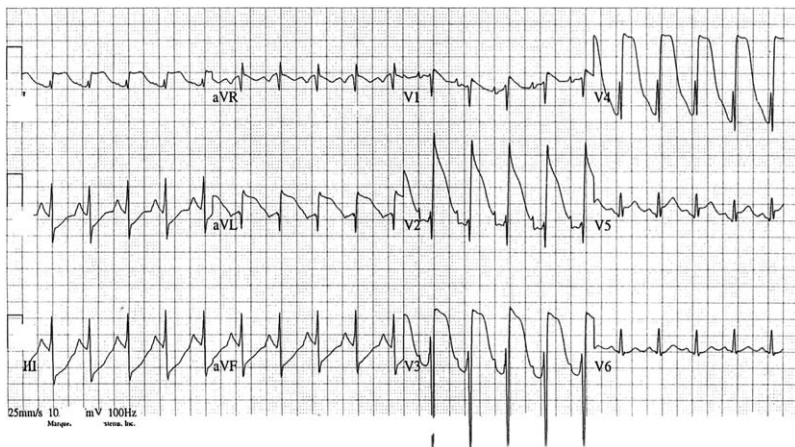


Fig. 1. Electrocardiogram of a 50-year-old woman who presented to the emergency room with an out-of-hospital cardiac arrest from ventricular fibrillation. She was resuscitated and the initial postresuscitation electrocardiogram is shown. She went to emergent cardiac catheterization where an intra-aortic balloon pump was placed for cardiogenic shock. Coronary angiography demonstrated normal coronary arteries in spite of the dramatic ST-segment elevation at the time of angiography. Upon return to the coronary care unit, neurologic examination revealed fixed and dilated pupils. An emergent head CT showed a massive subarachnoid hemorrhage.

with cardiac longer arrest time (8.0 minutes) [11]. In the same study, a resuscitation time leading to achieving ROSC with an average of 17 minutes was more likely to result in a favorable outcome than resuscitation time greater than 34.5 minutes [11].

Clinical evaluation

Cardiac and systemic evaluation

Postresuscitation cardiac examination should focus on blood pressure, heart rate, and clinical evidence of hypoperfusion, such as cool extremities and oliguria. Lung examination for edema also is important. Clinical cardiogenic shock is evident with blood pressure less than 90 mm Hg, pulmonary edema on examination, and evidence of hypoperfusion—all in the setting of acute myocardial infarction. Finally, detection of heart murmurs, such as aortic stenosis, and a comprehensive neurologic evaluation add important information. The ICU team and neurologist often work as a team in the early assessment of patients.

An electrocardiogram not only shows evidence of ischemia but also should be evaluated for prolongation of the QT interval, delta waves in Wolff-Parkinson-White syndrome, right ventricular overload seen with pulmonary embolism, hypertrophy and pseudoinfarction pattern seen in hypertrophic cardiomyopathy, and low voltage pattern with atrial enlargement seen with infiltrative cardiomyopathy.

Laboratory tests focusing on the cardiac cause, including standard electrolytes and magnesium, are determined and optimized. A toxicology screen should be sent on many patients, if the diagnosis is not immediately evident. Cocaine use is associated with cardiac arrest and myocardial infarction, the treatment of which differs from the treatment of typical coronary artery disease [13]. After resuscitation, most patients have evidence of cardiac enzyme elevation, including creatine kinase and troponin I or T. The sensitivity and specificity of troponin to diagnose myocardial infarction after successful ROSC in patients who have cardiac arrest are 96% and 80%, respectively [14].

For most patients admitted to an ICU after resuscitation for cardiac arrest, an echocardiogram early in the hospital course often gives useful information, such as overall left ventricular function; a wall motion abnormality consistent with myocardial infarction; valvular abnormalities, such as aortic stenosis; and the presence of a pericardial effusion. This information not only gives the clinician information about the possible cause of the cardiac arrest but also assists in management, particularly if hypotension is present.

Other potentially treatable conditions associated with cardiac arrest include acidosis, toxins, cardiac tamponade, moderate to severe hypothermia, hypoxia, poisoning, hyperkalemia, pulmonary embolism, and tension pneumothorax [1]. Routine testing, including examination, electrolytes, blood gas, and chest radiograph, often results in a correct diagnosis.

Another frequent diagnostic test obtained in the first 24 hours, depending on the clinician's index of suspicion, is CT imaging of the brain and lungs.

Neurologic evaluation

Many studies describe functional recovery in relation to the neurologic clinical function of patients resuscitated from cardiac arrest [15–20]. Many of the clinical findings of these studies are incorporated into the bedside practice of prognosticating functional outcome in this patient population. The interventions provided to patients in the studies describe the evolution of neurologic recovery, because the vast majority of these patients were subjected only to normothermic conditions. Therefore, the data derived from a normothermic population can be applied properly only to patients who are normothermic. With the development of effective therapies, such as hypothermia (see the article by Bernard elsewhere in this issue) and other potential therapies still being studied (see the article by Popp and Böttiger elsewhere in this issue), caution must be used when applying data from previous studies of dissimilar patient populations and interventions.

When evaluating neurologic injury in patients resuscitated from cardiac arrest, a complete bedside neurologic evaluation is essential consisting of evaluation of mental status, which needs to address patients' ability to arouse and engage in a meaningful interaction with the examiner. The cranial nerves have to be assessed appropriately in responsive and in unresponsive patients. Cranial nerve function and sensorimotor and other reflexes may provide critical insight into the extent of injury in unresponsive patients. Although the autonomic system may be affected largely by the cardiac arrest, certain neurologically relevant manifestations of the autonomic system are worth observing, such as the patterns of breathing, temperature, heart rate, and blood pressure. Breathing patterns may indicate injury to specific areas of injury at the level of the brainstem, whereas the occurrence of bradycardia and hypertension may suggest intracranial pressure (ICP) elevation or Cushing's reflex.

As clinical indicators of functional outcome, the neurological examination must be taken in the proper context of the overall clinical picture. Parameters that may confound findings on physical examination as predictors of poor outcome must be taken into consideration, however, including medications, especially sedatives and illicit drugs used before arrest; hypotension; focal cerebral ischemia; seizures; electrolyte abnormalities; hepatic or renal failure; and acidosis.

In 1985, a landmark study was undertaken by Levy and colleagues describing the neurologic findings of patients who were comatose after resuscitation after cardiac arrest [16]. A similar study was undertaken in 1994, in the multicenter BRCT, in relation to the assessment of neurologic prognosis in comatose survivors of cardiac arrest [18]. With more studies on this subject, Zandbergen and colleagues [15] provide a systematic review of the prediction of poor outcome in anoxic-ischemic coma.

In patients who are unresponsive after resuscitation from cardiac arrest, several neurologic findings may show some predictive value for functional outcomes at various times during the recovery period. Pupillary light reflex, brainstem reflexes, and motor response to pain are the best studied and most helpful clinical predictors of outcome [15,16,18]. In 1985, Levy and colleagues reported a 100% positive predictive value for predicting severe or worse outcomes if the pupillary light reflex was absent on the initial examination after resuscitation [16]. Subsequent studies show that that lack of pupillary light reflex immediately after resuscitation has a low specificity and not always is indicative of poor outcome [18–20]. As the absence of the pupillary light reflex in these patients becomes more persistent, especially on or after 3 days, the likelihood of a poor outcome approaches 100% [15]. Brainstem dysfunction as manifested by the absence of two or more brainstem reflexes (pupillary light response, corneal reflex and oculocephalic reflex) for more than 6 hours after arrest also are highly predictive of poor outcome [15]. Lack of oculocephalic reflex after 8 hours is highly predictive of poor outcome and its specificity improves at 24 hours [17].

Motor response to painful stimuli consistently is shown to be a reliable component of the physical examination of unresponsive patients [21,22]. Edgren and colleagues in 1994 [18] reported that lack of any motor response to painful stimuli at 3 days after arrest was the best and only independent predictor of poor outcome that could be identified.

Similar findings were reported [16] in patients who were unresponsive at 3 days and had no withdrawal or flexor motor response to pain. Investigators have tested the predictive value of the Glasgow Coma Scale (GCS) and find that a GCS score less than 5 for more than 2 to 3 days and the persistence of a GCS score greater than 8 for more than 1 week also are predictors of poor outcome [18,23]. GCS score reaches greatest specificity at 3 days [15].

Although 3 days is the traditional minimum time of observation in relation to the absence of pupillary light reflex and motor response, a meta-analysis by Booth and colleagues in 2004 reported that the absence of 5 clinical signs (absent corneal reflexes at 24 hours, absent pupillary response at 24 hours, absent withdrawal response to pain at 24 hours, no motor response at 24 hours, and no motor response at 72 hours) is sufficient to predict death or poor outcome as early as 24 hours [24]. The investigators also suggest that although useful signs occur at 24 hours after cardiac arrest, an earlier prognosis should not be made by clinical examination alone [24].

The absence of findings (pupillary light reflex, brainstem reflex, and motor response) may help determine poor functional outcome at 24 or 72 hours. This information is used routinely to aid in the decision of level and duration of care provided to these patients. The observation period is at least 24 hours; therefore, these parameters may have no relevance to neuroprotective therapies that ideally are provided acutely (within 24 hours) in the period of cardiac arrest and resuscitation. Also, no clinical findings are widely validated that provide health care providers with information that indicates the

likelihood of a favorable outcome in patients. Therefore, there still is a need to undertake research and identify early (within minutes or few hours of injury) neurologic markers of brain injury and recovery. These markers, if identified, may aid in the development of more effective therapies.

Optimizing survival and functional outcome in the ICU

Coronary revascularization and reperfusion in survivors of out-of-hospital cardiac arrest

Because the pathophysiology of cardiac arrest often involves plaque rupture and thrombosis [6], and because many patients, after resuscitation from cardiac arrest, evolve a myocardial infarction, emergent revascularization may benefit certain patients. This may be beneficial particularly in improving the left ventricular dysfunction that frequently is present after resuscitation. This concept of emergent coronary revascularization was evaluated in a prospective trial where a select group of out-of-hospital sudden death survivors underwent emergent angiography and possible percutaneous coronary intervention [25]. This study was conducted in Paris, France, where physicians staffed the ambulances. Successfully resuscitated patients between 30 and 75 years of age were eligible if there was no obvious noncardiac cause and the patients previously had been well. Of the 1762 cases of suspected out-of-hospital sudden cardiac arrest cases responded to by the ambulance study team, only 85 patients were eligible to be transferred for emergent cardiac catheterization. The majority of patients were excluded because of failure to resuscitate and fatal recurrent cardiac arrest while in transport. Of the 84 patients who underwent emergent angiography, 60 patients had significant coronary disease, with coronary artery occlusion found in 40 patients, and were treated with coronary angioplasty. The mean ejection fraction was significantly depressed at 34%. The two independent predictors of coronary artery occlusion on angiography in this select group of patients who had out-of-hospital cardiac arrest were ST-segment elevation on the admission electrocardiogram and chest pain before the arrest. The presence of one of these predictors had positive and negative predictive values for coronary artery occlusion of 0.63 and 0.74, respectively. The presence of chest pain before the arrest and ST-segment elevation on the electrocardiogram had a positive predictive value of 0.87 and negative predictive value of 0.61. Nine of 85 patients who demonstrated an occluded coronary artery on angiography had neither chest pain preceding the arrest nor ST-segment elevation on the admission electrocardiogram. Predictors of survival to hospital discharge included absence of inotropic drug support during transport and successful coronary angioplasty. A longer time from cardiac arrest to resuscitation was associated with worse survival. The poor predictive value of clinical and electrocardiographic data in predicting coronary occlusion on angiography is not surprising, given the frequent lack of history in comatose

patients and the many other causes of cardiac arrest that may be associated with significant ST changes [8]. One aspect of this study was that of the large number of cardiac arrests screened, only 1 in 20 subjects were taken to cardiac catheterization. This selection bias plus the lack of any data regarding whether or not routine percutaneous coronary intervention improves neurologic outcomes puts into question whether or not coronary angiography and percutaneous coronary intervention should be performed on an emergent basis in all patients surviving out-of-hospital cardiac arrests. As with any indication for an invasive procedure, the risks and benefits need to be individualized before proceeding to angiography. If methodologies progress such that an early and accurate determination that neurologic recovery in particular sudden death survivors is likely, a more aggressive approach to emergent coronary angiography likely will evolve.

Patients who have ST-segment elevation on electrocardiogram with hemodynamic compromise, such as cardiogenic shock, should be considered for emergent coronary angiography. A randomized trial in patients who had cardiogenic shock shows that an invasive approach with catheterization and coronary revascularization improves short- and long-term outcomes [26]. Other survivors of cardiac arrest who have ROSC and who should be considered for early angiography with possible coronary revascularization include those who have ST-segment elevation within 12 hours of symptom onset with evidence of or suggestion that neurologic recovery is likely.

Some small series and one underpowered randomized study of 35 patients who had out-of-hospital cardiac arrest evaluate whether or not thrombolytic therapy at the time of emergency room arrival improves outcomes [27]. The premise for this provocative therapy rests on the role of thrombus (coronary ischemia and pulmonary embolism) in the etiology of out-of-hospital cardiac arrest. Although these small studies suggest a possible benefit for some patients, a larger randomized placebo controlled trial shows no benefit using the fibrinolytic agent, tissue plasminogen activator [28]. In this study, 233 patients who had an out-of-hospital cardiac arrest and demonstrated 1-minute or greater pulseless electrical activity, despite initiation of standard cardiopulmonary resuscitation, were randomized to placebo or a 100-mg dose of tissue plasminogen activator. The primary endpoint was survival to hospital discharge, which occurred in one patient randomized to fibrinolytic therapy compared with no patients randomized to placebo. These data show the terrible outcomes in patients who have pulseless electrical activity and no benefit for fibrinolytic therapy in this patient group.

Associated risk of brain hemorrhage post systemic thrombolysis

Thrombolysis, either local or systemic, after resuscitation from cardiac arrest is a concern because of the potential increased risk of intracranial bleeding. Several uncontrolled studies find thrombolysis safe for the brain. A retrospective analysis reports on 68 patients who received systemic

thrombolytics after resuscitation from cardiac arrest for presumed acute myocardial infarction. Cardiac reperfusion was achieved in 71% of the patients treated. Intracranial hemorrhage was reported in only one patient, whereas four others had bleeding outside the central nervous system [29]. A study of the use of intravenous thrombolytics as therapy for brain injury after cardiac arrest currently is taking place in Europe. (See the article by Popp and Böttiger elsewhere in this issue for discussion of this therapy.)

ICU therapy

After resuscitation from cardiac arrest, admitted patients generally are intubated with varying degrees of mechanical ventilatory support and require general supportive measures in the ICU, such as sedation, deep vein thrombosis prophylaxis, and stress gastritis prophylaxis. In the absence of randomized clinical trials and treatment guidelines for many ICU conditions in these patients, this article discusses considerations for management based on existing literature and the authors' own clinical experience.

Hemodynamic instability

Many patients, after resuscitation from cardiac arrest, have significant hemodynamic lability. More than half of patients who are resuscitated require vasopressor support during the first 72 hours of their hospitalization [30]. Many of the early deaths in the ICU result from circulatory collapse. The cause of the hypotension often is multifactorial, including left ventricular dysfunction and inappropriate peripheral vasodilatation. The peripheral vasodilatation and left ventricular dysfunction result from the global ischemia and reperfusion that occur after cardiac arrest and resuscitation [31]. During reperfusion from an ischemic episode, as occurs during cardiac arrest, there is a dramatic release of oxygen-free radicals; activation of cytokines, complement, and neutrophils; and activation of endothelial surface adhesion molecules. Cytokine levels rise rapidly after resuscitation from cardiac arrest. In a series of 61 patients who had out-of-hospital cardiac arrest and ROSC, cytokine levels drawn on admission to the hospital were markedly elevated and comparable to the levels seen in patients who have septic shock [31]. In this study, cytokines, such as interleukin 6 (IL-6) and tumor necrosis factor α (TNF- α), correlate with the level of lactic acid on admission. Nonsurvivors and patients requiring vasopressor support had significantly higher levels of cytokines, such as IL-6 and TNF- α [31]. The elevation of cytokines was independent of any evidence of infection. Endothelial adhesion molecules for neutrophils also are up regulated rapidly after total body ischemia and reperfusion that occurs with ROSC after cardiac arrest [31]. Therefore, one mechanism of vasodilatory shock after ROSC in many patients who have out-of-hospital cardiac arrest and are admitted to an ICU is a systemic inflammatory response. This response is associated

with marked elevation of cytokines, such as IL-6 and TNF- α , which predict mortality. The correlation between lactic acid and cytokine levels suggests that one cause of this systemic inflammatory response is whole-body ischemia and reperfusion that occurs in cardiac arrest survivors.

Also contributing to circulatory collapse after ROSC after cardiac arrest is inappropriate nitric oxide expression and elaboration [32]. The expression of inducible nitric oxide synthase (iNOS) that is stimulated by cytokines contributes to the systemic inflammatory response and inappropriate vasodilatation. Observations in patients who have cardiogenic shock complicating an acute myocardial infarction show that systemic vascular resistance often is inappropriately low, whereas overall ejection fraction is not impaired horrendously [33]. After exposure to a variety of cytokines that are produced after ischemia and reperfusion, iNOS is expressed by many cell types. This can lead to toxic levels of nitric oxide and its metabolites, such as peroxynitrite. High levels of nitric oxide and nitric oxide metabolites directly inhibit myocardial function, suppress oxidative metabolism, reduce responsiveness to catecholamines, and induce systemic vasodilatation. Animal models support a role for iNOS and elevated nitric oxide levels contributing to the hemodynamic collapse seen in many patients who have ROSC after cardiac arrest. Inhibition of nitric oxide synthase improves left ventricular function in the ischemia and reperfusion mode [34]. Current human trials with nitric oxide synthase inhibition are ongoing to determine whether or not cardiogenic shock patients benefit from this therapy.

Hypotension

Transient left ventricular dysfunction, commonly present after ROSC from cardiac arrest, also contributes to the hypotension and vasopressor support often required in this patient population. This left ventricular dysfunction typically lasts 48 to 72 hours, followed by gradual improvement of the cardiac output [30]. The dose of epinephrine required for resuscitation is the primary factor that correlates best with postresuscitation left ventricular transient dysfunction. These data suggest that high levels of catecholamines cause transient left ventricular dysfunction or stunning and contribute to the transient shock often present in this patient population. These data are supported by the transient left ventricular dysfunction or stunning recently demonstrated in patients who have severe emotional stress [35]. Catecholamine concentrations in this population also are elevated, suggesting that endogenous and exogenous catecholamines can cause transient myocardial stunning, with improvement in left ventricular function during the next 48 to 72 hours.

In patients who have hypotension, a trial of volume expansion often is beneficial. Although in certain situations, pulmonary artery catheterization gives important information, routine management of hypotension with a pulmonary artery catheter generally is not indicated [36,37]. Randomized

trials in postsurgical patients, patients who are postmyocardial infarction, and patients who have critical illness show no benefit and possible worse outcome in those randomized to pulmonary artery catheterization compared with conventional therapy [37]. This adverse outcome may result from misinterpretation of the data from the pulmonary artery catheterization or overuse of vasopressor medications that can worsen ischemia and left ventricular function in patients who have depressed cardiac outputs. Selective use instead of routine use of a pulmonary artery catheter should be considered in patients who have ROSC and cardiogenic shock with hypotension, pulmonary edema, and depressed left ventricular function. In patients who do not respond to volume and low-dose vasopressors, placement of a pulmonary artery catheter also should be considered. If vasopressors are required for refractory vasodilatory shock, combination therapy with modest catecholamine infusion plus vasopressin is preferable to high doses of catecholamines. In a study of 46 patients who had vasodilatory shock requiring norepinephrine, patients were randomized to the addition of vasopressin versus continued escalation of norepinephrine doses. The former group had less tachycardia, fewer atrial arrhythmias, improved cardiac output, and better markers of organ perfusion [38].

The impact of hypotension on the progression of neurologic injury may affect functional outcome significantly. Persistent systemic hypotension leading to cerebral hypoperfusion can worsen neurologic outcome and should be avoided. Due to impairment of cerebral autoregulation in patients after cardiac arrest the ideal mean arterial pressure (MAP) range for brain preservation is not known [39]. Good functional neurologic recovery is associated positively with higher spontaneous arterial blood pressure during the first 2 hours after cardiac arrest [40].

Cardiac arrhythmia

Many patients admitted to an ICU have had an antiarrhythmic agent initiated either in the field or emergency department. A randomized trial shows that an amiodorone bolus of 300 mg is superior to placebo in shock-resistant ventricular fibrillation in patients suffering out-of-hospital cardiac arrest [41]. An amiodorone bolus also is superior to lidocaine in producing ROSC [42] and is the antiarrhythmic agent of choice in shock-resistant ventricular fibrillation. In patients who receive amiodorone therapy for out-of-hospital cardiac arrest with ROSC, there is a lack of randomized trial data concerning length of therapy with an antiarrhythmic agent. Nevertheless, continuing an intravenous infusion for 24 hours seems reasonable. Thereafter, the amiodorone generally can be stopped and not resumed unless recurrent and sustained ventricular arrhythmias become evident. Most sudden death survivors have coronary artery disease, with myocardial infarction present in a large percentage of patients. In addition, an enhanced adrenergic state contributes to ventricular fibrillation. Therefore, beta-

blockade should be initiated on admission to an ICU, if blood pressure and hemodynamics permit [43]. Beta-blockade is contraindicated in patients who have cardiac arrest and ROSC and who also have hypotension, significant bradyarrhythmias, and severe pulmonary edema.

Sepsis and temperature control

Sepsis occurs frequently in patients who have cardiac arrest. Two common sources of sepsis are aspiration during arrest and abdominal sepsis. The latter arises from the bowel ischemia as a consequence of ischemia and reperfusion. The majority of patients should have routine cultures performed on admission. In patients who are hypotensive after ROSC, physicians should consider the initiation of broad-spectrum antibiotics that cover lung and bowel flora until further culture data are available and hemodynamics improve.

As with sepsis, elevated body temperature occurs often. Increased body temperature after cardiac arrest is associated with worse outcome and brain death [44]. In a study of 40 patients, all 20 patients who had a peak axillary temperature above 39° within the first 72 hours after cardiac arrest became brain dead versus only 3 of 20 patients who had a peak temperature less than 39°C [44]. Considerations related to the cause of temperature elevation may have contributed significantly to the poor outcome, but with recent evidence that hypothermia is beneficial, the prevention of hyperthermia with routine antipyretics and cooling measures are important clinical interventions. In appropriate situations, therapeutic hypothermia can be instituted during the early period after cardiac arrest [45,46]. (See the article by Bernard elsewhere in this issue for discussion of this therapy.)

Coagulopathy

Frequently contributing to the postarrest syndrome and also mimicking sepsis is a coagulopathy. Many patients, after ROSC, have marked activation of blood coagulation without adequate activation of endogenous fibrinolysis. This can lead to microvascular thrombosis, resulting in further organ dysfunction [47]. The activation of the coagulation system also is related to the large increase in cytokines seen in patients who have ROSC after cardiac arrest. In a study of 67 patients admitted after out-of-hospital cardiac arrest with ROSC, measures of cytokines and coagulation were obtained [47]. Patients had increased IL-6, coagulation activity (elevated levels of thrombin-antithrombin complex), reduced anticoagulation (depressed antithrombin, protein C, and protein S), activated fibrinolysis (elevated plasmin-antiplasmin complex), and inhibited fibrinolysis (increased plasminogen activator inhibitor 1 levels). Activation of coagulation and fibrinolysis and reduced anticoagulation at admission were more pronounced in nonsurvivors, in particular patients dying in hospital of refractory shock. These data suggest that nearly all survivors of out-of-hospital cardiac arrest have a systemic

coagulopathy present on admission to the ICU, such as coagulation activation, diminished anticoagulant factors, or increased fibrinolysis. The coagulopathy likely originates from cytokine up regulation of tissue factor, known to be up regulated after cardiopulmonary resuscitation [48]. These coagulation abnormalities also may contribute to the high early mortality seen in those surviving out-of-hospital cardiac arrest. (See the article by Popp and Böttiger elsewhere in this issue for discussion of management consideration of this problem.)

Antiplatelet and anticoagulation therapies

Aspirin should be given on admission to the hospital and continued daily, unless contraindicated or clinical data exist that patients do not have obstructive coronary artery disease [49]. Full-dose anticoagulation with heparin is another consideration for patients after sudden cardiac death with ROSC. In general, patients who have possible or definite acute coronary syndromes from plaque rupture are anticoagulated with heparin for 48 hours after admission to the hospital [50]. This therapy reduces recurrent ischemic events. Initiation of full-dose anticoagulation depends on the clinical suspicion of an acute plaque rupture event resulting in ischemia, ventricular fibrillation, and sudden cardiac death. The bleeding risks of anticoagulation with heparin (chest trauma from cardiopulmonary resuscitation) versus the benefit of full-dose anticoagulation in patients who have acute coronary syndrome need to be considered carefully by clinicians. Heparin needs to be held until the coagulopathy, if present, resolves.

Seizures and myoclonus

Seizures and myoclonus are common after cardiac arrest, occurring in approximately one third of patients [51]. (See the article by Koenig and colleagues elsewhere in this issue for discussion of these clinical problems.) Clinical or electrographic seizure activity persisting more than 30 to 60 minutes usually, but not invariably, is associated with poor outcome [52–55]. Status epilepticus, the persistence of a seizure activity, often is considered a predictor of poor outcome, as is persistent myoclonus. Caution must be taken, however, in characterizing epileptic and myoclonic activity properly after arrest. Postanoxic myoclonus (Lance-Adams syndrome), previously regarded as a predictor of poor outcome, may improve as neurologic status improves [56]. (See the article by Venkatesan and Frucht elsewhere in this issue for description of this clinical condition.) Postanoxic myoclonus tends to be more common in patients who have respiratory causes of arrest. A state of status myoclonus, however, defined as more than 30 minutes of myoclonic activity associated with burst suppression on electroencephalogram (EEG) [53], which occurs commonly after cardiac arrest, is considered an indicator of extremely poor prognosis, and treatment with antiepileptics tends not to influence short-term or long-term outcomes [53,57]. Status

myoclonus tends to last only a few days. Differentiation between these two states can be difficult, but it is important to identify the difference. EEG monitoring and repeated evaluation may be helpful. Myoclonic status epilepticus, defined as myoclonic jerks merging with tonic-clonic seizures and lasting more than 30 minutes, is associated with failure to recover consciousness [17], although some investigators question this [58].

Seizures can delay the recovery of consciousness after cardiac arrest, and subclincial status epilepticus can depress the neurologic examination falsely and can be a cause for persisting unresponsiveness. An EEG should be obtained if seizures are suspected. Once seizures are found to occur, they should be treated aggressively to optimize recovery. Reports on the use of prophylactic antiepileptics therapy are limited, however, and not well clarified in the literature.

Cerebral edema and intracranial pressure elevation

Global cerebral ischemia may lead to brain edema. In one study, up to 47% of patients resuscitated from out-of-hospital arrest showed cerebral edema on head CT at day 3 [59]. In another study, more patients (92%) who had cerebral edema on head CT were noted among those who had primary respiratory arrest [59]. Cerebral edema can be quantified objectively by the degree of obliteration gray matter–white matter demarcation by brain CT scan [60]. Torbey and colleagues find that the progressive loss of gray matter–white matter demarcation as a reflection of brain injury is associated with poor outcome [60]. In these reports, brain edema is a marker of brain injury and associated with poor neurologic outcomes. (See the article by Geraghty and Torbey elsewhere in this issue for a detailed discussion of this approach at prognostication.)

Several small studies have attempted to define the occurrence of intracranial pressure elevation after resuscitation from cardiac arrest. In a study of ICP monitoring starting as early as 3 hours for a period of 2 to 7 days, ICP persistently remained below 20 mm Hg in five of the six patients. ICP elevation to 57 mm Hg was noted in one patient who had seizure activity. Although the study was limited by sample size, the absence of intracranial pathology or seizures made ICP elevation unlikely [61]. Another study showed that ICP elevation was associated with delayed hyperemia by transcranial Doppler ultrasound after resuscitation from cardiac arrest [62]. Therefore, the use of acute hyperventilation and mannitol therapy may be beneficial at the time of ICP elevation. These therapies are used successfully in other pathologies, but their use in edema related to global ischemia is not well described. Use of steroids does not provide benefit and can lead to adverse outcomes [63].

Hyperglycemia

Elevated serum glucose is associated with unfavorable outcome after global ischemia from cardiac arrest [63,64]. Serum glucose elevation is

believed to be a marker of the severity of injury. In a series of 145 nondiabetic patients evaluated after witnessed ventricular fibrillation cardiac arrest, a strong association between high median blood glucose levels during 24 hours and poor neurologic outcome was found [65].

Elevation of serum glucose after acute neurologic injury may be harmful, therefore treatment of hyperglycemia in patients who have nonlacunar stroke, and global ischemia is advocated [66]. In the absence of controlled human trials showing the benefit of glucose control in patients resuscitated from cardiac arrest, some insights may be taken from the general critical care literature. Although the precise effect of elevated glucose on neurologic injury of patients who have postcardiac arrest remains not well defined, tight glucose control is associated with improved survival and outcome in patients who are critically ill [67]. Until a dedicated controlled clinical trial in the specific area is undertaken, glucose monitoring in the ICU is strongly suggested, and providing tight control may provide benefits to patients who have postcardiac arrest.

Age and systemic complications

Many victims of cardiac arrest are elderly and have serious underlying comorbidities [9]. A review of noncardiac complications in cardiac arrest survivors notes that the most frequent complications are pneumonia, electrolyte abnormalities, and gastrointestinal hemorrhage in approximately 45%; followed by seizures and elevated liver enzymes in approximately 28%; and septicemia, acute renal failure, and acute respiratory distress syndrome in approximately 5% to 7% of patients [68]. Although advanced age (older than 65) is a risk factor for decreased overall survival after cardiac arrest, age is not an independent risk factor for poor neurologic outcome [12]; therefore, age consideration should be taken into account as plans for therapy are undertaken.

Future directions in the ICU

Much of the injury resulting in hemodynamic instability, cardiac dysfunction, and brain injury results from ischemia and reperfusion injury. Animal models demonstrate that many therapies given before ischemia and reperfusion improve outcomes. Naturally, pretreatment is impossible in patients after cardiac arrest. Several therapies currently in clinical trial may improve cardiac function in the setting of ischemia and reperfusion [69]. Certainly, therapies already demonstrated to reduce reperfusion injury, such as hypothermia, need to be applied more widely. Future technologies that assess neurologic prognosis more readily and accurately will assist in patient selection for early coronary angiography. Continued research in the identification of high-risk patients for sudden cardiac death may result in better preventative strategies [70].

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