

Chapter 9

Cardiac Arrest



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9.1 Introduction

The human brain is dependent upon the delivery of oxygen and glucose and the removal of waste products for normal activity with the interruption of this cycle resulting in tissue injury. A reduction of oxygen content within the brain parenchyma is the state of anoxia, while the cessation of blood flow is ischemia. There are many different etiologies of anoxia including a reduction in blood flow—stagnant anoxia; lack of oxygenation—hypoxic anoxia; insufficient oxygen transport—anaemic anoxia; and a disturbance in the intracellular oxygen transport—histotoxic anoxia. In adults the most common cause is a combined hypoxic and ischemic injury caused by cardiac arrest.

For a neurological disease state with such high prevalence, surprisingly little is understood about the precise patterns of impairment or about the natural history of recovery. There are robust early predictors of outcome of anoxic-ischemic coma (Nolan et al., 2015; Wijdicks, 2006), but the outcome has rarely been specified beyond good, poor, and death.

This chapter is designed to examine the etiology, pathology, neurological sequelae, treatment, and outcome of patients who survive a cardiac arrest.

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9.2 Epidemiology and Clinical Burden

Cardiac disease has been the leading cause of death in the United States since 1921, currently accounting for 30% of all deaths (Minino & Smith, 2001). In 1998 in the United States, 456,076 deaths, or 63% of all cardiac disease deaths were caused by cardiac arrest (Zheng, Croft, Giles, & Mensah, 2001)—a 7% increase over the previous 10 years. The average age of the cardiac arrest patients is approximately 65 years (Eisenburger et al., 1998; Kuilman, Bleeker, Hartman, & Simoons, 1999). Estimates of short-term survival from large population surveys of patients who have undergone resuscitation for cardiac arrest vary from 1.4% (Becker, Ostrander, Barrett, & Kondos, 1991; Lombardi, Gallagher, & Gennis, 1994) up to 20% (Fischer, Fischer, & Schüttler, 1997; Kuisma & Maata, 1996; Sedgwick, Dalzeil, Watson, Carrington, & Cobbe, 1993; Waalewijn, de Vos, & Koster, 1988). The best survival rate in the United States of about 15–20% comes from a suburban community in Washington State (Cummins, Ornato, Thies, & Pepe, 1991; Rea, Eisenberg, Becker, Murray, & Hearne, 2003), while the worst is the urban communities (Gaiieski et al., 2017; Lombardi et al., 1994). With a mean survival rate of 8% (Chan, McNally, Tang, Kellermann, & CARES Surveillance Group, 2014), there would be 36,500 survivors of cardiac arrest every year in the United States alone. The long-term survival of these patients has been reported as 70–85% at 1 year (Chan et al., 2016; Fischer et al., 1997; Graves et al., 1997; Kuilman et al., 1999; Sedgwick et al., 1993), 66% between 2 and 5 years (Ladwig et al., 1997), 52% at 3.5 years (Earnest, Yarnell, Merrill, & Knapp, 1980), 44–77% at 5 years (Graves et al., 1997; Kuilman et al., 1999), 73% at 7 years (1999), and 18% at 10 years (Graves et al., 1997). Improvement in medical care has resulted in a steady increase in survival (Rea, 2003; Smith, Andrew, Lijovic, Nehme, & Bernard, 2015; Wong et al., 2014) and neurological outcomes (Chan et al., 2014) over time.

Chart reviews (Graves et al., 1997), telephone interviews (Ladwig et al., 1997), and neuropsychological testing (Roine, Kajaste, & Kaste, 1993) on patients who have survived a cardiac arrest have shown that one-quarter to two-thirds of all survivors have neurological deficits, and one-half of all survivors have cognitive or motor deficits of a magnitude that requires a major lifestyle change (Bergner, Hallstrom, Bergner, Eisenberg, & Cobb, 1985; Earnest et al., 1980; Graves et al., 1997).

Based on the reported rates for survival and impairment, we would estimate a yearly incidence of approximately 5/100,000 (12,000) survivors of cardiac arrest who will have persistent neurological deficits and a rolling prevalence of 50,000 impaired survivors in the United States. This is roughly equivalent to the number of patients diagnosed with multiple sclerosis in the United States every year (National Multiple Sclerosis Society, 2005). These numbers are increasing with the improvement of the “chain of survival” concept (Cummings et al., 1991), implementation of disease modifying therapy (The Hypothermia after Cardiac Arrest Study Group, 2002), and further refinement of the implantable defibrillator (Hlatky, Saynina, McDonald, Garber, & McClellan, 2002). This improvement also reflects an

improvement in neurological outcomes (Chan et al., 2014). For example, a nationwide study in Japan (Kitamura et al., 2012) demonstrated a near doubling (from 1.6% to 2.8%) of favorable neurological outcomes in 2009 compared to 2005.

9.3 Neuropathology

During a cardiac arrest, brain tissue can survive for about 4–5 min without oxygen and blood before irreversible damage occurs (Bass, 1985). The severity of brain damage is dependent upon the duration of ischemia, the degree of ischemia, the core temperature, and the blood glucose level (Auer & Benveniste, 1994). Even though cardiac arrest causes global ischemia and hypoxia, neuronal injury is maximal in specific focal regions, a concept known as selective vulnerability. For reasons still not entirely understood, the small- and medium-sized neurons of the striatum, the Purkinje cells of the cerebellum, the layer III neurons of the cerebral cortex, and thalamic neurons are the first areas to show degenerative changes (Auer & Benveniste, 1994; Kuroiwa & Okeda, 1994). The pyramidal neurons of the hippocampal formation may not show the earliest damage but undergo delayed neuronal death (Horn & Schlote, 1992; Petito, Feldmann, Pulsinelli, & Plum, 1987). The etiology of this delayed neuronal death is unknown, but factors thought to play a role include the intracellular formation of oxygen free-radicals and excessive neuronal excitability because the hippocampal pyramidal neurons are at the end of a major excitatory pathway (Auer & Benveniste, 1994; Murayama, Bouldin, & Suzuki, 1990).

There have been several studies on the temporal sequences of cell death after anoxia. Horn and Schlote (Horn & Schlote, 1992) examined the brains of 26 cardiac arrest patients and found the earliest damage occurring in cortical layers three, five, and six, appearing within the first few days. Purkinje cell necrosis was observed up to day 6. Rapid hippocampal pyramidal neuronal cell death was seen from days 4 to 7. Petito et al. (1987) found a similar pattern in their review of 14 cases and concluded that the cortex and basal ganglia suffered early damage (occurring within the first 18 h) while the hippocampus suffered delayed necrosis at greater than 24 h.

The pathology literature is dominated by patients who suffered a severe anoxic injury and early death. Little is known about possible regionally specific brain pathology in patients suffering less severe anoxia. Although selective vulnerability is the accepted theory to account for the patterns and distribution of neuronal damage and patterns of clinical impairment, the precise relationship between pathology and clinical signs is incompletely understood.

Hypoxic–ischemic damage to specific regions of the brain is, nevertheless, certainly responsible for the diverse, specific neurological deficits. Immediate (hours to days) complications of cardiac arrest include death, coma (Levy et al., 1985; Yarnell, 1976), severe encephalopathy (Sawada et al., 1990), seizures (Madison & Niedermeyer, 1970), myoclonus (Lance & Adams, 1963), and cortical blindness

(Sabah, 1969). Long-term complications include persistent vegetative state (Sazbon, Zabreba, Ronen, Solzi, & Costeff, 1993; Yarnell, 1976), diffuse injury (Parkin, Miller, & Vincent, 1987), amnesic syndrome (Volpe & Hirst, 1983), frontoexecutive dysfunction (Armengol, 2000; Reich, Regestein, Murawski, DeSilva, & Lown, 1983), visuospatial dysfunction (Howard, Trend, & Ross Russell, 1987; Kase, Troncoso, Court, Tapia, & Mohr, 1977), pyramidal tract weakness (Allison, Bedford, & Meyer, 1956), extra-pyramidal disorders (Hawker & Lang, 1990), ataxia (Lance & Adams, 1963), spinal cord infarct (Silver & Buxton, 1974), and other very rare disorders. The frequency of each of these complications and whether they co-occur in any particular pattern are not known. Whether the course of recovery or specific outcome conditions (other than death) is tightly related to the severity of the hypoxic–ischemic event is unknown. It is also unknown if any pattern of early deficits is systematically linked to long-term sequelae.

For the clinician, there are several levels of importance: (1) predicting acute survival as a basis for judgment about intensive support, (2) managing and predicting short- and long-term recovery among survivors, (3) recognizing the range of residual deficits and the implications for specific vulnerability, and (4) working knowledge of the utility of proposed treatments.

9.4 Acute Prediction of Survival and Quality of Recovery

The bulk of outcome prediction research was collected before the advent of targeted temperature management (TTM). While targeted temperature management improved survival (Bernard et al., 2002; The Hypothermia after Cardiac Arrest Study Group, 2002), it was initially unclear how it affected outcome prediction (Nielsen et al., 2013). Pooled data suggests that TTM incurs a survival and neuroprotective benefit (Schenone et al., 2016). It has also become clear that it impacts the prognostic utility of clinical examination and laboratory testing. TTM may alter or delay the course of neurological recovery, and hence, the timing of assessing prognosis remains unknown. Validated protocols for assessing outcomes following TTM are rare, biased by withdrawal of care (Gold et al., 2014; Mulder et al., 2014), and in the absence of a standard consensus protocol, continue to rely on pre-temperature management data.

9.4.1 Examination

There is no measure of injury that has proven uniformly informative about severity. Duration of anoxia, time to CPR and defibrillation, or cause of cardiac arrest accurately does not predict the outcome (Wijdicks, 2006), although one study showed

that >99% of patients with favorable outcomes, defined as cerebral performance category¹ (CPC) of 1–2, had CPR of less than 35 min (Goto, Funada, & Goto, 2016).

Only about 25% of out-of-hospital cardiac arrest patients survive to hospital admission (McNally et al., 2011), with approximately 25% awake (Longstreth, Inui, Cobb, & Copass, 1983). Relying on the level of consciousness to predict outcome, Longstreth et al. (1983) found that of those patients who awakened after 24 h, 73% had cognitive or motor deficits. After 4 days of coma, no patient ever fully recovered. This predictive method may not apply to those who have not received targeted temperature therapy because several recent studies have found that over 80% of patients who received targeted temperature therapy who awakened after 72 h were discharged with a CPC 1–2 (Gold et al., 2014; Grossestreuer et al., 2013). While this may not be a true discrepancy since CPC of 1 includes patients with minor neurological deficits, there are reports of patients in coma for greater than 7 days, who received TTM, with good outcomes (Greer, 2013; Grossestreuer et al., 2013). Other studies confirmed that the early awakens generally have good outcomes with only between 13% and 23% having any motor or cognitive deficits compared to 52% and 73% of the patients awakening after 12 h having deficits (Earnest, Breckinridge, Yarnell, & Oliva, 1979; Snyder et al., 1980). Sazbon et al. (1993) and others (Estraneo et al., 2013) followed patients with a history of 30 days or more of unconsciousness for at least 5 years and found that not a single patient recovered to a state of moderate disability or better.

The most straightforward and predictively useful applied evaluation is the clinical examination. The critical aspects of the acute, clinical examination are description of the depth of coma and the status of the critical vegetative brainstem functions. Assessment of coma may be complicated by intensive care management. The reliance on using the neurological examination to predict neurological outcome was initially based on the work by Levy et al. (1985). They and others (Edgren, Hedstrand, Kelsey, Sutton-Tyrrell, & Safar, 1994; Zandbergen et al., 2006) have shown that the absent pupillary light reflex after 24 h has a 100% positive predictive value (PPV) for a poor outcome. The sensitivity of this test is only around 20%. Subsequent to TTM, there have been reports of patients who did not have one or more brainstem reflexes at day 3 (Bouwes et al., 2012; Dragancea et al., 2015; Rossetti, Oddo, Logroscino, & Kaplan, 2010) with good outcomes (CPC 1–2). An automated pupillometry approach may ultimately have the best predictive value in assessing outcomes (Solari et al., 2017).

Absent motor response to painful stimuli at 72 h is a more sensitive test (around 60%) with two pre-TTM class I studies (Edgren et al., 1994; Levy et al., 1985) having a PPV of 100%, but (Zandbergen et al., 2006) five out of 105 patients with absent motor responses at 72 h were awake after 1 month in the most recent class I

¹Cerebral performance category: CPC of 1 indicates good cerebral performance but may have minor psychological or neurological deficits. CPC of 2 indicates moderate cerebral disability typically resulting in impairment of activities of daily living. CPC of 3 is severe cerebral disability with dependence upon others for daily support. CPC of 4 is coma or vegetative state, and CPC of 5 is death.

study. The motor response appears to have been most affected by TTM (Al Thenayan, Savard, Sharpe, Norton, & Young, 2008; Dragancea et al., 2015; Rossetti et al., 2010) and is no longer felt to be a useful predictor of poor outcome.

9.4.2 *Laboratory Studies*

Prolonged cardiac arrest results in metabolic cell death with the release of intracellular contents, and recent studies have explored the utility of assays of brain enzymes as a potential marker of injury severity and outcome. Studies have focused on serum neuron-specific enolase (NSE) (Karkela, Bock, & Kaukinen, 1993; Schoerhuber et al., 1999; Zandbergen et al., 2006), serum astroglial S100 (Pfeifer et al., 2005; Zandbergen et al., 2006), brain-type creatine kinase isoenzyme (Karkela et al., 1993; Karkela, Pasanen, Kaukinen, Morsky, & Harmoinen, 1992), and CSF lactaid (Edgren, Hedstrand, Nordin, Rydin, & Ronquist, 1987). These studies indicate that serum NSE levels >33 $\mu\text{g/L}$ between days 1 and 3 following cardiac arrest most accurately predicts poor outcome with a PPV of 100% and sensitivity around 50%, but again, its predictive value has diminished post-TTM with debates on the cutoff value and timing (Bouwes et al., 2012; Oksanen et al., 2009; Rundgren et al., 2009; Tiainen, Roine, Pettilä, & Takkunen, 2003). One small study showed that abnormal serum astroglial S100 levels at day 3 was associated with low test performance in attention, memory, and executive function (Prohl, Bodenburg, & Rustenbach, 2009).

Recently, an offshoot of the Targeted Temperature Management study (Nielsen et al., 2013) used a novel assay to detect serum levels of axonal injury maker tau in 689 cardiac arrest patients (Mattsson et al., 2017). They found that at 72 h, serum tau levels above 72.7 ng/L had a PPV of 100% in predicting poor outcome (CPC 3–5) with a sensitivity of 42%. Reducing the cutoff to 13.4 ng/L brought up the sensitivity to 65% with a false-positive rate of 1%. Tau did not appear affected by TTM, and low levels or decreasing levels from 24 h to 72 h may predict a good outcome (CPC 1–2), although sensitivity and specificity were not discussed.

Serum tau has the potential to be a more practical test because it may have utility in other disease such as traumatic brain injury (Liliang et al., 2010; Ost et al., 2006) and dementia (Shekhar et al., 2016). These tests currently offer little practical utility because many hospitals cannot provide rapid turnover of these test results.

9.4.3 *Electrophysiology*

Electroencephalography (EEG) and somatosensory evoked potentials (SSEP) supplement the clinical examination and laboratory tests as predictive measures of poor outcome. Generalized suppression, burst suppression, or generalized periodic

complexes on a flat background EEG patterns within the week of admission almost invariably resulted in death or vegetative state (Edgren et al., 1987; Rothstein, Thomas, & Sumi, 1991; Scollo-Lavizzari & Bassetti, 1987), although in a single study, two patients with malignant EEG had a good recovery (Chen, Bolton, & Young, 1996). TTM has likely altered the predictive value (or timing) of EEG because the most recent large group analysis demonstrated a false-positive rate of 1.5% (Rossetti et al., 2017) in patients with highly malignant EEGs.

Specific seizure types can also portend a grim prognosis. Initially, several controlled studies have shown that the presence of myoclonic status epilepticus within the first 24 h has grim prognosis (PPV of 100%) (Wijdicks, Parisi, & Sharbrough, 1994; Zandbergen et al., 2006), although there has been a case report of a survivor of myoclonic status epilepticus (Arnoldus & Lammers, 1995). A lack of a clear standard definition of myoclonic status epilepticus continues to cloud prognostication, as some papers have relied on the clinical presence of sustained myoclonus (Arnoldus & Lammers, 1995; Wijdicks et al., 1994) regardless of EEG correlation. When outcomes were examined in post-TTM patients with myoclonus with or without EEG evidence of seizures, those patients with corresponding poor EEG (suppression-burst background with spike-wave discharges in lockset with myoclonic jerks) had a much poorer prognosis (Elmer et al., 2016), but even with these stricter criteria, 1% of these patients have good outcomes (Seder et al., 2015).

Absent SSEP within the first week was also predictive of poor recovery. The only class I study (Zandbergen et al., 2006) and six class III studies (Bassetti, Bomio, Mathis, & Hess, 1996; Berek et al., 1995; Chen et al., 1996; Gendo et al., 2001; Logi, Fischer, Murri, & Mauguire, 2003; Madl et al., 2000) observed that no patient with bilaterally absent N20 response ever recovered. A single class III study (Young, Doig, & Ragazzoni, 2005) had a false-positive rate of 6%. A meta-analysis of these eight studies (Wijdicks, 2006) demonstrated a PPV of 99.3% with a sensitivity around 50%. Post-TTM studies have generally supported SSEP as a highly specific predictor of poor outcomes (Bisschops, van Alfen, van der Hoeven, & Hoedemaekers, 2011; Bouwes et al., 2009; Leithner, Ploner, Hasper, & Storm, 2010; Rossetti et al., 2010; Tiainen, Kovala, Takkunen, & Roine, 2005) with a few controversial good outcomes (Bouwes et al., 2012; Dragancea et al., 2015).

An earlier meta-analysis and recent comparative, prospective study by a group in the Netherlands (Zandbergen et al., 2006; Zandbergen, de Haan, Stoutenbeek, Koelman, & Hijdra, 1998) evaluating various early prediction of poor outcome, including clinical examination, brain enzymes, and electrophysiology, demonstrated that absence of SSEP at any time within the first week was the most useful predictor of poor outcome. This has been validated (Geocadin et al., 2006) showing that this was the clinical parameter most relied upon by neurologists to estimate prognosis.

9.4.4 Neuroimaging

Imaging is frequently obtained in survivors of cardiac arrest, but to date, there is no datum on the utility of these modalities to predict outcome in survivors of cardiac arrest. While highly informative, the subjective interpretation and day-to-day variability in abnormalities (Greer et al., 2011) has diminished imaging's utility as a reliable outcome prognosticator. Early CT findings of comatose patients revealed diffuse cerebral edema and occasional low densities in the basal ganglia, thalamus, or watershed distributions (Fujioka, Okuchi, Sakaki, Hiramatsu, & Iwasaki, 1994; Kjos, Brant-Zawadzki, & Young, 1983). MRI in comatose cardiac arrest patients using fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted (DW) imaging demonstrated early signal abnormalities in the cerebral cortex, cerebellum, thalamus, and hippocampus (Wijdicks, Campeau, & Miller, 2001), and in the cerebral white matter (Chalela, Wolf, Maldjian, & Kasner, 2001). (See Fig. 9.1 for a representation of images of a comatose survivor of a cardiac arrest who died 3 days later.)

Not surprisingly after a direct metabolic injury to neurons, there is a significant reduction in brain metabolic activity in patients with acute cardiac arrest. Mean cerebral glucose utilization in vegetative or comatose subjects is reduced by 38% (Roine et al., 1991) to 50% (DeVolder et al., 1990), compared to a 25% reduction in conscious patients. The reduction is in the watershed distributions of the cerebral cortex, the basal ganglia, and the thalamus. Progressive decline of oxygen metabolism may foretell prolonged coma (Edgren, Enblad, Grenvik, & Langstrom, 2003).

Although non-randomized and non-prospective, these imaging studies do offer some useful markers of a bad outcome (death or severe disability): brain swelling on CT scan on day 3 (Morimoto, Kemmotsu, Kitami, Matsubara, & Tedo, 1993), extensive abnormalities on MRI DWI and FLAIR images (Wijdicks et al., 2001), and >50% perfusion deficits of the supratentorial brain on SPECT scan (Roine et al., 1991). The converse is less useful: structural imaging may be normal in patients who will survive with substantial neurological deficits (Alexander, 1997; Carbonnel, Charnallet, David, & Pellat, 1997; De Renzi & Lucchelli, 1993; Rupright, Woods, & Singh, 1996; Speech, Wong, Cattarin, & Livecchi, 1998).

More recently the use of quantitative image analysis at around day 3 can be used as adjunctive information to improve diagnostic accuracy in predicting poor outcome while maintaining specificity using CT measurements (Kim et al., 2013; Wu et al., 2011) or DWI analysis (Hirsch et al., 2016; Kim et al., 2016; Wijman et al., 2009; Wu et al., 2009). Analysis of thresholds remains variable and subjective; thus, its use as a stand-alone prognosticator has not been demonstrated. The advent of resting-state functional connectivity MRI analysis may hold promise because preliminary studies have demonstrated a reduction in the default mode connectivity, maybe associated with poor outcome (Koenig et al., 2014; Norton et al., 2012).

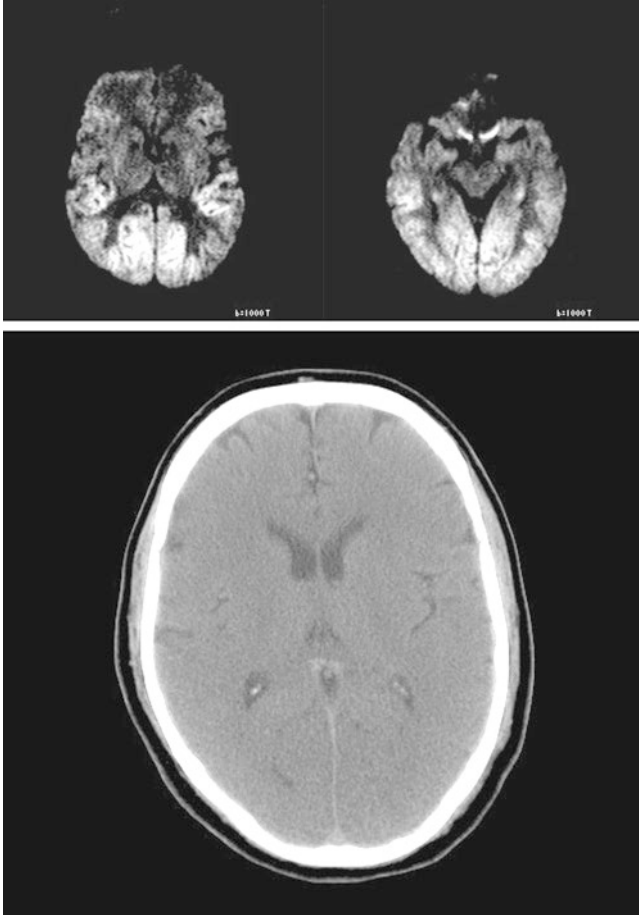


Fig. 9.1 Diffusion-weighted MRI images (a, b) and CT image of a 53-year-old man who suffered a 30-min cardiac arrest. Diffusion images reveal areas of restricted diffusion within the entire cerebral cortex. CT scan shows evidence of gross edema with effacement of sulci and loss of grey/white matter junction

9.4.5 Summary

The recent study by the Netherlands group (Zandbergen et al., 2006) also examined whether the predictive values of various tests and clinical findings were additive in increasing sensitivity. They found that the combination of the SSEP and NSE raised the sensitivity to 66% and the addition of EEG (burst suppression or worse pattern) increased it to 71% while maintaining 100% PPV.

The current recommendations from the American Academy of Neurology (Wijdicks, 2006), updated by the European Resuscitation Council (Nolan et al., 2015) involves a decision tree using the variables pupillary light reflex, corneal

reflex, motor response to pain, myoclonic status epilepticus, NSE, and SSEP to aid in the prediction of outcome in survivors of cardiac arrest. This algorithm involves the near certain prognosis of a poor outcome with absent brainstem reflexes (pupillary and corneal reflexes) or absent N20 responses on the SSEP after 72 h, and the likely prognosis of a poor outcome with the presence of status myoclonus, unreactive burst suppression or worse on EEG, or elevated serum NSE after 72 h. Even with the adoption of this algorithm, the sensitivity remains poor.

There remains no clinical finding or test result that reliably predicts a good outcome.

9.5 Course of Recovery

Caronna and Finklestein (1978) have proposed that patients in coma for less than 12 h suffer from a reversible encephalopathy and usually make a rapid and complete recovery, whereas the more severe hypoxic–ischemic patients are in coma for longer than 12 h and suffer structural damage to specific brain regions. In regard to time to awakening, several studies (Earnest et al., 1979; Longstreth et al., 1983; Snyder et al., 1980) found that 15–27% were awake upon arrival to the hospital and 20–43% of survivors would awaken after 12 h. The most common recovery pattern was of early in-hospital awakening to a confusional state to clearing of cognitive deficits (at least overt ones) during the hospitalization (Levy et al., 1985; Longstreth et al., 1983; Snyder et al., 1980). This has been supported by anecdotal case reports of patients progressing from coma to reportedly normal within 24 h (Sabah, 1969) and of isolated amnesic syndromes recovering over 10 days (Finklestein & Caronna, 1978).

As outlined above, there is a fairly inviolate relationship between duration of coma and the quality of recovery. For coma greater than 4 days, the probability of a good outcome falls dramatically (Longstreth et al., 1983). Patients who present comatose who do not wake up will progress to brain death or vegetative state, a state of wakefulness without detectable awareness (Jennett & Plum, 1972). A vegetative state present 1 month after brain trauma is defined as a persistent vegetative state (Multi-Society Task Force on PV, 1994). Among all nontraumatic causes, 53% die, 32% remain in persistent vegetative state, and 15% recover consciousness (1994). Of those who awoke, only 1 out of 15 had a good outcome, but the underlying etiology of that one patient was not clarified. The remaining 14 were severely disabled, many with minimal communication at best and all dependent (Higashi et al., 1981). Estraneo et al. (2013) followed 43 anoxic patients for 2 years after entering persistent vegetative state and found only 9 awoke, all with severe disabilities. Thus, contrary to traumatic brain injury, all patients who remain unresponsive for more than 1 month following anoxic brain injury have poor outcomes.

For those who awaken, the course of recovery is, however, similar for all injuries, except for the severe injuries—slower and incomplete. All patients awaken, that is,

their eyes open, marking the end of coma in the narrowest sense. More mildly injured patients progress almost immediately into a confusional state. More severely injured patients remain vegetative—eyes open, random eye movements without fixation, and without any directed responsiveness—before moving into a confusional state.

Confusional states are conditions of impaired attention with or without impaired arousal. They are characterized by reduced ability to sustain attentional focus, easy distractibility, poor registration of new information, and defective recall of experience. Patients are often agitated. Sleep is often disrupted. Over hours to weeks, depending on severity, confusion clears, that is, attention improves. Only when confusion has cleared, can the nature and severity of residual deficits be judged.

Determination of the overall distribution of severity of residual deficits will be influenced by the timing and setting of patient accrual, and by the measure of severity. One prospective study of patients in coma for at least 12 h (Caronna & Finklestein, 1978) demonstrated 3-month mortality of 60%, severe disability or vegetative state of 20%, moderate disability of 8%, and good recovery of 12% (30% of all survivors). Differences in “moderate” and “mild” probably reflect differences in measures used. Another prospective study included patients who had already survived at least 3 weeks and were medically stable enough to be evaluated for definitive cardiac management. The percentages with good recovery was 28% at initial (3 weeks) evaluation, 43% at about 2 months, and 71% at 6 months (Sauve, Doolittle, Walker, Paul, & Scheinman, 1996). This study suggests that there exists a subgroup of patients who will have some late recovery. In a retrospective, population-based chart review, Graves et al. (1997), using the poorly sensitive cerebral performance category (CPC), revealed that after 1 year 29% of patients in CPC3 and 77% of patients CPC2 improved by at least one performance category. Case reports also mention severely impaired patients who make remarkable recovery within the first 1–3 months of injury (Goh, Heath, Ellis, & Oakley, 2002; Kam, Yoong, & Ganendran, 1978; Kaplan, 1999). Contrary to the above studies, Kim et al. (2016), also relying on the CPC, showed that only 4% of their patients improved from CPC 3 to CPC 2 over the first 6 months, and none improved after 6 months.

Patients admitted to rehabilitation centers will be the ones with persistent significant deficits once medically stable, but not such severe deficits that they cannot participate in therapies. The point of initial assessment will usually be 2–4 weeks after arrest. Fertl, Vass, Sterz, Gabriel, and Auff (2000) observed that 35% of their patients, all with CPC of 3, improved one performance category and 10% improved two categories during the 3-month rehabilitation. They also noted an improvement of the mean Barthel index of all their patients from 28 to 61. At time of discharge from rehabilitation hospital, 35% had moderate and 55% had severe deficits. Roine et al. (1993) traced cognitive recovery, albeit with a very coarse instrument for this purpose, the Mini Mental State Exam, and found very little change after 3 months. Others have noted no improvement after 4 months (Groswasser, Cohen, & Cosfeff, 1989) or 8 months (Drysdale, Grubb, Fox, & O’Carroll, 2000). We prospectively

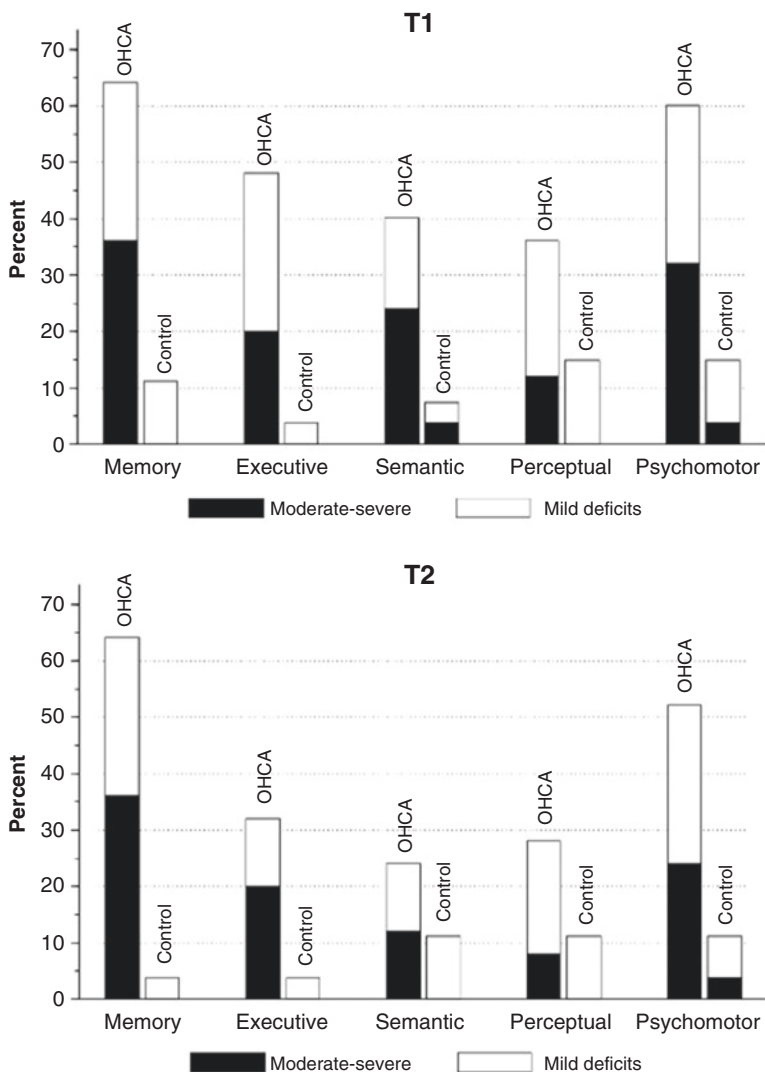


Fig. 9.2 Neuropsychological deficits at 3 months (T1) (a) and 12 months (T2) (b) post-injury. Percentage of out-of-hospital cardiac arrest (OHCA) and control patients with mild (z -scores between -1 and -2) or moderate-severe (z -scores ≤ -2) deficits in each domain

followed 25 survivors for 1 year and noted (1) the bulk of the recovery occurred within 3 months, (2) there was no further recovery of memory function after 3 months (see Fig. 9.2), (3) memory performance predicted quality of life (Lim, Verfaellie, Schnyer, Lafèche, & Alexander, 2014).

9.6 Residual Deficits

The focus of this discussion will be on the cognitive deficits because those are almost universally most limiting. The majority of the literature consists of case reports motivated by interest in the cognitive impairment rather than the range of neurological consequences of cardiac arrest. Some investigators were indifferent to the etiology of the hypoxic event. Most group studies followed the same approach, with only a few examining the patterns, frequency, and natural history of the survivors of cardiac arrests. In some reports, there was a broad latitude in the diagnosis of a hypoxic event, and in others, multiple etiologies of hypoxia were considered together without isolating the cardiac arrest patients from other etiologies. We will describe the specific persistent cognitive impairments that have been reported as well as where those impairments fit into the more common characterization of arrest outcomes by severity.

The case reports examining some aspects of cognition after cardiac arrest do offer some insight into the nature of possible impairments. We found 22 case reports with 39 patients who suffered an uncomplicated cardiac arrest (Table 9.1). There were two cases presenting with virtually unique clinical syndromes, one with loss of semantic knowledge (Alexander) and the other with delayed dystonia (Boylan). There were three cases with cognitive deficits in a single domain, with two amnesic (Cummings and Volpe) and one with visual perceptive problems (Rizzo). Based on the clinical description of the cases, we arbitrarily divided the patients into three categories: mild, moderate, or severe. One case had no deficits, nine cases had multiple deficits of moderate severity, and 12 cases had severe deficits. The remaining 12 cases had insufficient clinical or neuropsychological information to categorize. A large number of case reports did not have an isolated cardiac arrest.

The patients in the moderate-injury category presented with a very wide range of signs and symptoms. Coma duration ranged from 15 min to 1 week. Some awoke with no initially reported neurological abnormalities (Reich, case 6), and others were confused and disoriented (McNeill). All patients had deficits in more than one domain.

Of the 12 severe cases, eight reported coma duration, and all were comatose for more than 24 h. Two other cases were confirmed to have been in coma, but the duration was not provided. All four patients whose emergence from coma was described had a severe confusional state. All patients had deficits in every domain tested, although not all domains were tested or discussed in each case report.

The group studies, in contrast to the case reports, offer population-based information, but often lack detailed neuropsychological evaluations and frequently involved a mixed population. Roine et al. (1993) observed that the most common deficits among 68 consecutive survivors of cardiac arrest at 3 months were disorders of memory (49%), visuoconstructive dyspraxia (43%), and dyspraxia (42%), followed by problems with motivation (37%), depression (35%), programming of activity (34%), and dyscalculia (31%). Language disorders were uncommon (3%). The high frequency of memory disturbances has been confirmed by others, with

Table 9.1 Summary of case reports of survivors of isolated cardiac arrest

Study	Case	Age/ sex	Time to testing	Coma	Category	M	FE	VS	EPS	MO	C	S	L
Alexander		43/M	1 month	5 days	Severe	++	-	+		+			+
Allison	5	41/M		Yes	Severe		+	+					+
	6	19/M			Mod			+		+			+
Armengol	2	45/M	13 months	42 hours	Severe	++	++	++		+			
	5	47/M	15 months	15 days	Severe	++	++	++		+			
Barnes		46/F	1 year	24 hours	Mov	+			++				
Bengtsson	1	54/M	3 years		N/A	+		+					
	2	78/M	3 years		N/A	+	+	+					
	3	70/M	3 years		N/A	+	+	+					
	6	60/M	2.5 years		N/A	+		+					
	9	54/F	2 years		N/A	+	+	+					
	11	73/F	1.5 years		N/A	+	+	+					
	12	58/M	1 year		N/A	+	+	+					
	13	74/M	1 year		N/A	+	+	+					+
	15	81/F	10 months		N/A	+	+						
	18	63/F	7 months		N/A		+						
Boylan		50/M	2 years		N/A				++	+			
Bruni		56/M	1 month	4 days	Severe		+		+	+	+		
Carbonnel		55/M	1 year	1 week	Severe	+		++					+
Cummings		53/M	3 months		Amn	++	+	-		+			-
Dalla Barba		57/F	5 months	6 hours	Mod	++	++						-
Feve	4	34/M	1 month	1 week	Mod			+	++	-			
Lance	1	64/F	8 years	4 days	N/A				+		+		
	2	62/M	4 years	3 days	Mod	+			+		+		
McNeill		49/F	6 years		Mod	++	+	-		+			
Norris	4	49/M	6 months	5 days	Mild								
	5	41/M	11 months	Days	Severe		+	+	+	+	+	+	+
Parkin		43/F	1 year	16 days	Severe	+	+	+	+		+		+
Reich	1	48/M	2 years	Hours	Mod	++	+						
	2	41/M	2 years	15 months	Mod	++	+						
	3	39/M	2 years	20 hours	Mod	++	+						
	6	56/M	6 months	24 hours	Mod	+	+						
Rizzo	1	65/M			Vis	-		++					
Ross		58/M	3 years	Yes	Severe	++	++	+					+
Rupright	1	40/M	2 years		Severe	+	+	+					
	4	31/F	1 month		Severe			+					
Silver	5	54/M	2 months	24 hours	Severe	+							+
Szlabowicz		43/M	1 month	8 days	Severe								
Volpe	2	42/M	18 months		Amn	++	-	-		+			-

Abbreviations: *M* memory deficit, *FE* frontoexecutive deficit, *VS* visuospatial deficit, *EPS* extrapyramidal deficits, *MO* motor deficits, *C* cerebellar deficits, *S* spinal deficits, *L* language deficits, *Mod* moderate, *Diff* diffuse, *Amn* amnesic syndrome, *Vis* isolated visuospatial deficit, *Mov* isolated movement disorder

+ Neurological deficit by report or mild deficit verified by neuropsychological testing

++ Substantial neurological deficit verified by neuropsychological testing

- No neurological deficit by report or verified by single neuropsychological testing

-- No neurological deficit verified by two or more neuropsychological tests

ranges from 80% (Grubb et al., 2000) to 100% of patients examined (Kotila & Kajaste, 1984; Pusswald, Fertl, Faltl, & Auff, 2000). Visuospatial impairments have also been common, occurring in 30–100% of these patients. None of these studies specifically examined executive functions.

Wilson (1996) performed neuropsychological assessments in 18 survivors of cerebral hypoxia to explore for consistent cognitive profiles. Equipped with an unusually balanced battery of neuropsychological tests for this literature, she identified five distinct patterns: (1) an amnesic syndrome; (2) memory and executive deficits; (3) memory, executive, and visuospatial deficits; (4) isolated visuospatial impairments; and (5) widespread cognitive deficits. With the analysis restricted to survivors of cardiac arrests, there were three profiles: (1) memory and executive deficits; (2) memory, executive, and visuospatial deficits; and (3) widespread cognitive deficits. There were no isolated amnesic or visuospatial syndromes in her pure cardiac arrest patients, which seemed to occur more frequently from other causes of anoxia. Her patient population was small, but if isolated cognitive deficits occur after cardiac arrest, they must be at a very low frequency.

Volpe, Holtzman, and Hirst (1986) has reported the largest series of patients with isolated amnesia after cardiac arrest. These six patients had memory quotients at least 20 points below full-scale IQ, with normal performance on Ravens Progressive Matrices, the Wisconsin Card Sort task, and the Controlled Oral Word Association test. Clinical data, raw scores, and measures of motor control, mood, or behavior were not reported, but these patients appear to represent a pure amnesic syndrome.

It would seem likely that chronically amnesic patients might have hippocampal atrophy, and more diffusely impaired patients might have cortical atrophy. This hypothesis has been explored, although there are limitations because so many of the arrest survivors have implanted defibrillators now and cannot have an MRI. Grubb et al. (2000) compared MRI-brain volume in memory impaired and memory intact survivors of cardiac arrest. They did not find selective hippocampal atrophy in their memory impaired patients. Reduction in whole brain volume significantly correlated with memory impairment. Hopkins and colleagues have done MRI volumetric on a number of anoxic patients. In a series of papers comparing anoxic patients to controls, they (Hopkins & Kesner, 1995) found a reduction in hippocampal areas but not temporal lobe or parahippocampal gyrus volume. Another study (Hopkins et al., 1995) did suggest a relationship between morphological abnormalities with performance on cognitive testing, but was limited to three patients. The largest study comprised 13 patients, of whom only five had had a cardiac arrest, showed a strong correlation between performance on anterograde memory tests with both hippocampal and regional gray matter volume residuals (Allen, Tranel, Bruss, & Damasio, 2006).

We had the opportunity to study 11 cardiac arrest patients under the age of 80 years who were referred to a memory disorder clinic for persistent memory deficits (Lim, Alexander, LaFleche, Schnyer, & Verfaellie, 2004). Using standardized neuropsychological tests, we assessed their memory, executive function, perception, language and, motor function (see Table 9.2). Ten of our patients had moderate to severe memory impairment, and five had severe executive impairments. There

Table 9.2 Neuropsychological testing domains of 11 patients who has suffered an isolated cardiac arrest: mean z-scores or number of tasks on which performance was abnormal

Patient	Memory (z-score)	Executive (z-score)	Boston naming (z-score)	Perceptual impairment	Motor (z-score)
1	0.4	0.5	0.9	0/3	-1.0
2	-2.6	-0.6	0.1	0/3	-3.3
3	-2.5	-0.5	0.2	1/3	-2.1
4	-3.3	-1.8	-0.1	1/3	-5.0
5	-3.3	-1.2	-1.4	0/3	-2.1
6	-2.0	-1.2	0.8	0/3	-3.8
7	-3.2	-2.8	-1.2	0/3	-2.9
8	-6.5	-2.9	-2.4	0/3	-8.0
9	-3.1	-4.8	-5.1	3/3	-10.0
10	-3.5	-2.6	-9.5	2/3	-1.3
11	-3.6	-3.1	-2.7	1/3	-2.8

was only one patient impaired in lexical-semantic function and only one with perceptual difficulties. Nine patients had moderate to severe impairments in motor function. We performed a k-means cluster analysis which produced a three-cluster solution that yielded a cluster with no impairments (patient 1), a second cluster with memory and motor impairments and variable executive dysfunction (patients 4–6), and a third cluster with impairments in all domains (patients 7–11). No patient had an isolated neurological disorder.

Our patient 1 and the small number of case reports with no deficit or only subtle deficits presumably exemplify the largest outcome group of survivors of cardiac arrest. These patients with good recovery usually emerge early from coma. Whether the neural injury was entirely transient and reversible, or simply too mild to cause lasting deficits is unknown. As with our patient, there may be relative decrements in performance that are obscured by arbitrary cutoffs on tests, or functional deficits that are not detectable by neuropsychological testing. These patients are likely to be underrepresented in the literature.

Patients in our cluster 2, the four patients reported in the Wilson's study with memory and executive deficits (Wilson, 1996), and several of the case reports reviewed above uniformly had intermediate outcomes. The relationship between duration of coma and outcome is quite variable. We propose that these patients have not suffered permanent widespread cortical damage and may have damage restricted to the selectively vulnerable brain regions. To our knowledge, this hypothesis has not been directly addressed in any autopsy or adequately sensitive anatomical study. Our patients all had memory and motor impairments. We believe that executive deficits would also consistently have been detected if this group had been evaluated sooner after emergence from coma and confusion.

The patients in our cluster 3 and many of the patients whom we categorized as severe from case reports have similarly poor outcomes. These patients usually have long periods of coma (>24 h). In addition to memory and executive impairments,

language and visuospatial functions are disturbed, suggesting that the injury likely involved cortex as well as the more vulnerable subcortical and hippocampal regions. Motor deficits might have been prominent if they had been consistently assessed.

Neither the results from our patient group nor a critical review of the literature support the notion that isolated disorders of visual perception or memory occur frequently following cardiac arrest. Thus, the evidence that classic, abrupt CA results in isolated damage to the hippocampus and produces long-standing isolated amnesia is much weaker than commonly assumed. This is not to conclude that it cannot happen because there are descriptions of amnesia following cardiac arrest. We propose, however, that the residual deficits in most patients who survive cardiac arrest will fall along a continuum reflecting the severity of injury to those electively vulnerable sites. Impairment will range from no or subtle impairments to a mix of executive, learning, and motor control deficits to such severe executive deficits that all cognitive functions are impaired—a virtual, chronic confusional state. Intermixed within these patterns are the rare cases of isolated memory or visuospatial deficits, or unusual presentations such as semantic memory loss or delayed dystonia.

9.7 Treatment

9.7.1 *Temperature Management*

In 2002, two studies showed that 24 h of therapeutic hypothermia (TH) within the first 4 h of a cardiac arrest will improve overall outcome and survival (Bernard et al., 2002; The Hypothermia after Cardiac Arrest Study Group, 2002). The improved outcomes may not be the result of hypothermia, rather the avoidance of hyperthermia (Gebhardt et al., 2013; Nielsen et al., 2013; Zeiner et al., 2001), although the general evidence still supports the use of TH (Arrich, Holzer, Havel, Müllner, & Herkner, 2016; Schenone et al., 2016). Current consensus guidelines advocates for the maintenance of temperature between 32 and 36 °C, now known as targeted temperature management (Nolan et al., 2015).

There are several distinct epochs of management, each with its own treatment imperatives. There are few therapeutic interventions that directly affect the outcome of survivors of out-of-hospital cardiac arrest. Pharmacological interventions that have proven to be ineffective include nimodipine (Roine et al., 1993), thiopental (Brain Resuscitation Clinical Trial I Study Group, 1986), magnesium and/or diazepam (Fatovich, Prentice, & Dobb, 1997; Longstreth, Fahrenbruch, & Olsufka, 2002), sodium bicarbonate (Vukmir & Katz, 2006), and amiodarone and lidocaine (Kudenchuk et al., 2016).

As described above, patients emerge from coma into vegetative states or confusional states. There are no clinical studies of potential treatments for vegetative state after cardiac arrest. Confusional state is usually a transient condition during recovery, and in milder injuries, it may be rapid enough that no treatment issues emerge.

If there is a treatment concern, it is usually agitation. There are no controlled studies of treatment of agitation in this condition. Most adequately controlled studies are in the dementia literature. There are a few basic clinical observations that may assist management of confusion/agitation.

First, confusion and agitation are not synonymous. Treatment of confusion is probably limited to control of the environment around the patient—avoidance of over-stimulation, readily observed orientation material (calendars, clocks, pictures), and vigorous regularization of sleep phases. These should be implemented in every patient. Treatment of agitation should be modulated to the level of distress or inadvertent danger of injury that the patient presents. When possible, use of distractions may be sufficient—visits from family members, opportunities to converse with anyone on staff, recreational activities such as playing cards with a volunteer, watching sports on TV, etc. When the patient is very distressed, possibly becoming in inadvertent danger of injury or disruption of essential medical care, then supervision, passive restraints, and medications are required.

Second, the treatment targets of sleep onset and maintenance and of agitation reduction are not the same. Reduction of agitation should not produce excessive sleep or else sleep phases will become abnormal, probably worsening agitation. Second-generation antipsychotics such as quetiapine and olanzapine probably offer the best proportion of tranquilizing without excess sedation. Sleep onset is a separate problem, probably best addressed with standard hypnotics such as trazodone and short half-life benzodiazepines, but these medications will fail at sleep onset in a patient who is agitated, so they may require a preparatory dosage of antipsychotic to achieve a calm enough state that the hypnotic will be effective. Hypnotics should not be repeated too late at night or there will be further disruption of sleep phases due to daytime somnolence. Thus, management may require both treatments, each targeted at a specific factor.

For patients with significant residual deficits, there is at present little direct treatment. We could not identify any controlled studies or even large case reports of late rehabilitation interventions. We are aware of the off-label use of cholinesterase inhibitors, stimulants, and dopaminergic medications but with minimal sense of success and no reported claims of success. To judge by the reports of Grosswasser and Wilson described above—both reports coming from respected cognitive rehabilitation centers—there is little optimism that the fundamental deficits can be treated behaviorally. Whether patients with executive impairments after cardiac arrest might respond to some of the behavioral strategies that have been implemented in patients with trauma or focal frontal lesions is unknown.

There are many obstacles to the construction of useful interventions for these patients. We are not entirely clear about the nature of the residual deficits. Are they fundamentally executive function deficits? If so, there is a reasonable possibility of importing useful behavioral and medication treatments from the larger literature on treatment of trauma and focal lesions. When do they stabilize? How malleable are they over the post-acute epoch? Or do the patients who do not recover quickly also always have true memory system (hippocampal) injury as well? If so, behavioral treatments are likely to be insufficient to achieve any functional improvement. Until

treatments become more effective or until acute management discovers a biological intervention that prevents acute cell death and apoptosis, there will be a growing population of inadequately treated patients at risk for poor quality of life.

9.8 Quality of Life

Impairment does not necessarily lead to disability and handicap, but the reported effects on quality of life have been variable. We found that coma duration of greater than 3 days or presence of memory impairment at 3 months were associated with reduced quality of life (Lim et al., 2014). Cardiac arrest survivors fare significantly worse in all categories of their QOL compared to a random control population (Bergner, Bergner, Hallstrom, Eisenberg, & Cobb, 1984), and when compared to survivors of myocardial infarcts (Bergner et al., 1985; Lim et al., 2014). de Vos, de Haes, Koster, and de Haan (1999) showed that the quality of life of their cardiac arrest survivors were worse than an elderly control population, but better than that of patients with strokes. An 8-year follow-up of cardiac arrest patients found that the quality of life in patients was considered good (Kuilman et al., 1999), but the study lacked age-matched controls.

Evaluating the number of patients able to live independently or return to work may be the most sensitive markers of impairment, disability, and handicap. As many as 30–75% of survivors who awaken early are able to return to their previous level of employment (Bergner et al., 1985; Earnest et al., 1980; Graves et al., 1997; Kragholm et al., 2015; Sauve, 1995; Sunnerhagen, Johansson, & Herlitz, 1996). On the other hand, only 25% of patients who remain in coma for greater than 12 h return to work (Lim et al., 2014), while in those admitted to rehabilitation hospitals, fewer than 10% return to work (Groswasser et al., 1989; Howard et al., 1987). Approximately one-half of all survivors achieve full independence in all aspects of daily living (Earnest et al., 1980; Howard et al., 1987; Sunnerhagen et al., 1996) although many require substantial supervision and assistance for instrumental activities, finances, and social activities (Sauve, 1995). There is no datum on return to driving.

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