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Long-term neurological outcome after cardiac arrest and therapeutic hypothermia☆

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ABSTRACT

Aim of the study: To analyse the neurological status of survivors after cardiac arrest (CA) treated with hypothermia.
Methods: We prospectively included all patients with CA treated with hypothermia at intensive care units (ICU) in two university hospitals and one regional hospital. All adult survivors at 6 months after CA, $n = 48$, were invited for neurological follow-up and 43 accepted. History, clinical status, ability testing and questionnaires were administered to screen for difficulties, including Assessment of Motor and Process Skills, Neurobehavioral Cognitive Status Examination, Frontal Lobe Assessment Battery, EQ-VAS quality of life scale, Skåne Sleep Index, Hospital Anxiety and Depression Rating Scale, Self-reported Montgomery and Åstrand Depression Rating Scale, Global Deterioration Scale, Rivermead Behavioural Memory Test, and the Cerebral Performance Categories (CPC).
Results: No patient was found to be in a chronic vegetative state and all patients were living at home, one with extensive help. Thirty-six patients were in CPC1 at follow-up, and some degree of neurological sequelae was found in 40 patients, but was mild in all but 3. Three patients had no subjective complaints, nor could any deficits be detected. Initial defects improved over-time. Short-term memory loss, executive frontal lobe dysfunction along with mild depression and sleep rhythm disturbances were the most common findings.
Conclusions: Mild cognitive impairment is common following hypothermia-treated cardiac arrest but has little effect on activities of daily living or quality of life.

1. Introduction

Neurological sequelae in survivors after cardiac arrest (CA) constitute a major cause of handicap and illness.[1–3] The high energy utilization and limited energy stores render the brain particularly vulnerable to interrupted circulation, with a narrow margin of minutes until definite damage to brain tissue occurs.[4] A large number of therapeutic interventions have been tried, but all have failed to prolong the time until definitive damage occurs or to minimize the effects.[5] Based on two controlled randomized trials[6,7] therapeutic hypothermia (TH) has been recommended and implemented as a means of brain protection. In the larger of these two studies, 55% of patients treated with TH survived with good neurological outcome vs. 39% in the group that received conventional treatment.[6] In a sub-group of patients from this study, 67% of survivors were found to be cognitively intact 3 months following cardiac arrest.[8] Our study was initiated to make a detailed analysis of the types and the extent of neurological defects in survivors after CA after the implementation of TH as standard treatment in our hospitals. As it was considered unethical not to initiate TH based on the favourable results from the two randomized controlled studies and current treatment recommendations,[9] no untreated group was enlisted for direct outcome comparison.

Abbreviations: AMPS, Assessment of Motor and Process Skills; CA, cardiac arrest; CI, confidence interval; CPC, Cerebral Performance Categories; EQ-VAS, Euro Qol Visual Analogue Scale; FAB, Frontal Lobe Assessment Battery; GCS, Glasgow Coma Scale; GDS, Global Deterioration Scale; HADS, Hospital Anxiety and Depression Scale; ICU, intensive care unit; MADRS-S, Self-reported Montgomery and Åstrand Depression Rating Scale; NCSE, Neurobehavioral Cognitive Status Examination (Cognistat); OPC, Overall Performance Category; OT, occupational therapist; RBMT, Rivermead Behavioural Memory Test; RLS, Reaction Level Scale; ROSC, return of spontaneous circulation; SSI, Skåne Sleep Index; TH, therapeutic hypothermia.

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Table 1
Patient characteristics.

Hospitals	1 + 2 + 3	1	2	3
Patients	94	74	13	7
Age (years)	66 (14–87)	66 (14–87)	69 (37–84)	62 (48–83)
Sex (male)	64 (68%)	52 (70%)	8 (62%)	4 (57%)
Out-of-hospital CA	81 (86%)	62 (84%)	13 (100%)	6 (83%)
Witnessed	84 (89%)	64 (86%)	13 (100%)	7 (100%)
Initial rhythm				
VT/VF	65 (69%)	49 (66%)	10 (77%)	6 (83%)
ASY	17 (18%)	13 (18%)	3 (23%)	1 (17%)
PEA	8 (9%)	8 (11%)		
Unknown	4 (4%)	4 (5%)		
CA to ROSC (min)	18 (2–180)	20 (2–180)	14 (5–24)	14 (5–28)
CA to <34.0 °C (min)	210 (80–670)	210 (80–670)	180 (125–665)	195 (120–475)

Numbers are given as counts and percentages. Continuous variables are given as median and range. CA—cardiac arrest; VT/VF—ventricular tachycardia/ventricular fibrillation; ASY—Asystole; PEA—pulse-less electric activity; ROSC—return of spontaneous circulation. Time from CA to ROSC hospital 1 vs. hospitals 2 + 3 ($p = 0.035$; Mann–Whitney *U*-test).

2. Material and methods

2.1. Inclusion criteria for cooling

Patients with a witnessed or unwitnessed CA, irrespective of initial rhythm, cause or location, who were successfully resuscitated with a return of spontaneous circulation (ROSC). Patients eligible for TH were unconscious (Glasgow Coma Scale, GCS < 7) until the time for initiation of the cooling procedure (within 240 min from the CA).

2.2. Exclusion criteria for TH

Primary coagulation defect and terminal illness, CA secondary to aortic dissection, intracranial haemorrhage or other massive bleeding.

2.3. Patients

Patients were consecutively recruited from three hospitals at different time periods. Hospital 1, university clinic and regional referral centre for 24 h cardiologic interventions from February 2003 to October 2005, with $n = 74$, cooled, $n = 37$ surviving at time for follow-up. Hospital 2, university clinic, from September 2002 to September 2003, with $n = 13$, cooled, $n = 8$, surviving at time for follow-up. Hospital 3, a regional hospital, from January 2003 to November 2003, with $n = 7$, cooled, $n = 7$ surviving at time for follow-up. Patient characteristics for the entire cohort are displayed in Table 1. All patients were unconscious (GCS ≤ 7) at the time of cooling, which was introduced by cold saline 4 °C, 30 mL/kg and maintained at a core temperature of 33 °C over 24 h using an external cooling device or intravenous cooling as described earlier.[10,11] Patients were sedated immediately prior to and during cooling with fentanyl (1–2 μg/kg) and midazolam (0.05 mg/kg) and maintained with fentanyl (1–2 μg/kg/h) and propofol (2–4 mg/kg/h). Non-depolarising muscle relaxant, rocuronium, was used intermittently as needed to avoid shivering. Invasive cardiac interventions were performed irrespective of the phase of cooling.

2.4. Inclusion criteria for follow-up study

Surviving patients at 6 months after CA from the three participating hospitals were referred from the ICU and contacted for a neurological follow-up. Two patients were residing at a remote location and two abroad, one abstained. Four patients were not referred from the ICU. The nine patients that were lost to neurological follow-up were all contacted by an intensivist at 6–12 months after CA for CPC scoring. Eight of these were scored CPC 1 and one CPC 2. In total 43 patients participated in the neurological follow-up at a mean of 7.2 months after CA. The majority of patients were seen between 5 and 10 months following CA (91%) However, one patient was seen already after 3 months and three patients after 11, 13 and 14 months respectively due to practical reasons.

2.5. Assessment protocol

A screening assessment was designed in order to detect various likely difficulties and to distinguish various brain regions affected by global ischemia. The programme consisted of screening procedures for overall cognitive functions, the NCSE, Neurobehavioral Cognitive Status Examination (Cognistat),[12] which includes questions similar to the Mini Mental Status Examination, and assesses in addition various functions and abilities resulting in a profile over 10 domains. No sum score is given, but age-adjusted cut-off limits exist. The number of deviations from normal is given, along with the severity of the deviation. The categories that are evaluated include wakefulness, degree of orientation, alertness, and language. The AMPS, Assessment of Motor and Process Skills, is a standardized and validated activity assessment test,[13] which takes into account the subject's ability to perform tasks defined to be within a subjects daily praxis, performed under new circumstances. The ability to resolve the practical and functional adjustments necessary to complete the task is assessed from a procedural and motor aspect. An individual score for motor and processing skills is obtained after a scoring by an occupational therapist (OT). This is processed through a Rasch analysis to generate a cut-off level and an individual score. The test has a high reliability and internal consistency.[14] The Frontal Lobe Assessment Battery, FAB, is a bedside test designed to indicate lesions within the frontal lobe. A series of six questions and procedures are rated to give a sum score of in total 18, and numbers below 15 were considered to indicate a lesion and 12 or less a severe lesion.[15] A test aimed at assessing memory abilities in every day life, the RBMT, Rivermead Behavioural Memory Test, version II,[16] generates a screening score and a profile score and is graded as normal, mild, moderately or severely affected memory. It is correlated with patients' and family members' estimation of memory defects.[17]

Questionnaires, with subsequent discussion about the self-reported symptoms were used to screen for signs and symptoms indicating poor sleep, the SSI, Skåne Sleep Index (a local modification of the Pittsburgh Sleep Index),[18] anxiety, the HADS, Hospital Anxiety and Depression Scale,[19] and depression, the MADRS-S, Self-reported Montgomery and Åstrand Depression Rating Scale.[20] Finally a self-assessment of global cognitive difficulties, GDS, Global

Table 2
Cerebral Performance Categories (CPC) scale.

CPC 1: Good cerebral performance: conscious, alert, able to work
CPC 2: Moderate cerebral disability: conscious, can carry out independent activities
CPC 3: Severe neurological disability: conscious, dependent on others for daily support
CPC 4: Coma or vegetative state
CPC 5: Dead

Table 3
CPC scores at months in all treated patients.

Hospitals	All	1	2+3	2	3
CPC 1	41	26	15	8	7
CPC 2	9	9	0	0	0
CPC 3	2	2	0	0	0
CPC 4	0	0	0	0	0
CPC 5	42	37	5	5	0
Good outcome (CPC 1–2)					
All rhythms	53%	47%	75%	62%	100%
VT/VF	63%	56%	81%		
ASY, PEA, unknown	31%	28%	50%		

For definition of Cerebral Performance Categories score (CPC) 1–5, see Table 2. VT/VF—ventricular tachycardia/ventricular fibrillation. Good outcome in all patients hospital 1 vs. hospitals 2+3 ($p = 0.028$). Good outcome in VT/VF patients, hospital 1 vs. hospitals 2+3 ($p = 0.083$). VT/VF was strongly associated with good outcome compared to other initial rhythms ($p < 0.0005$).

Deterioration Scale, gives an overall score from 1 to 6 (1 = no self-perceived cognitive difficulties, 6 = severe),[21] and a short self-assessment of the quality of life (based on a visual analogue scale) is given as a %, Euro Qol Visual Analogue Scale (EQ-VAS).[22] At the time of evaluation the CPC categories 1–5 (Table 2) were estimated.[23]

Patients were seen by an OT who performed a structured interview on daily activities, performed the tests assessing levels of activity and functioning (AMPS, RMBT, NCSE, FAB) and instructed and aided patients in the questionnaires (EQ-VAS, GDS, HADS, MADRS-S, SSI). A board certified neurologist made a careful neurological assessment, including detailed history, neurological examination and CPC rating. The procedures took a maximum of 120 min in total. Due to language difficulties and other medical reasons, not all patients could complete all tests but response rates were in all tests >95%.

2.6. Statistical analysis

Descriptive statistics were employed throughout, with mean, medians, ranges or 95% confidence interval (CI) given when appropriate.

2.7. Institutional review board

At the time of inclusion for the cooling, next-of-kin gave first oral and later written consent for treatment and aspects of the protocol that involved study parameters. At the time of referral for follow-up, all patients gave written informed consent according to regulations by the Regional Ethics Review Board at Lund University Hospital.

3. Results

The proportion of survivors at the time of follow-up was 55.3%, $n = 52/94$. All surviving patients were CPC scored, see Table 3. The majority of survivors (50/52) had a good outcome, defined as CPC 1–2, only two patients scored CPC 3 and no patient was in a vegetative state (CPC 4). Good outcome was more common in patients with ventricular tachycardia/ventricular fibrillation (VT/VF) as initial rhythm and in patients from hospitals 2 and 3. Length of ICU-stay did not differ significantly between patients in CPC 1 and CPC 2+3 ($p = 0.104$).

Neurological follow-up was performed in 43 patients. Demographics of the assessed patients at time of follow-up were: 34 men, 9 women, mean age 62.4 years (range 18–85). Mean number of years in school 9.6, 36 with Swedish as native language. All were living at home, one with extensive help.

At the time of CA, 24/43 patients were retired, unemployed or on sick-leave due to cardiac disease or other disorders, and 19 were employed full-time. At the follow-up time point, 4 of the 19 were fully employed again, 4 had part-time work and 11 were on sick-leave. Of the remaining 24 patients 3 had required social support aid, and the remaining had unchanged social circumstances being retired or already previously being unemployed. In total nine patients had undergone some type of rehabilitation due to neurological symptoms after the CA.

The motor neurological status examination, was unremarkable in 36/43 patients. Only one patient required extensive support from personal assistants throughout day and night. This patient and another required wheel-chair after the CA, and a third patient was in wheel-chair prior to the CA due to a traumatic spinal lesion. One patient had severe speech and swallowing difficulties after the CA event, and four had either spastic gait, or focal partial paresis (arm/hand) that interfered with function. One patient had developed seizures after the CA but was seizure-free on medication. One patient had developed myoclonic jerks requiring medication, but the symptoms had declined over-time and were mildly disabling at the follow-up time point. One patient had a non-debilitating stroke after the CA, unrelated to any obvious cardiac cause. One patient suffered a massive local haemorrhage in one eye during the resuscitation and invasive treatment resulting in permanent blindness in this eye.

The mean and median values of the self-estimated cognitive difficulties in the GDS, was mean 2.09 (95% CI ±0.95), and median of 2, with 44.2% of the patients rating themselves as 1 = no cognitive difficulties, see Table 4a. In the FAB screening 62.5% reached normal values whereas 37.5% had indications of frontal lobe impairment with executive dysfunction and lack of inhibition, see Table 4b. The mean value was 14.6 (95% CI ±4.0) and a median of 15.5. In the RMBT one third of the patients had moderate to severe memory difficulties, with a mean score of 18.1 (95% CI ±6) and a median of 19, see Table 4c.

In the cognitive screening test NCSE, 20/42 (48%) patients scored within age-adjusted limits, 10/42 (23.8%) had a mild defect. Sixteen patients scored moderate difficulties in singular domains only. Only one had severe orientation difficulties, and one had a severe calculation defect. Six patients had severe memory difficulties in this test and one patient had three severely affected scores, see Table 4d.

In the AMPS test of motor abilities, 9/38 (24%) fell below a cut-off limit of 2.0. For the processing skills, 8/38 (21%) patients scored below the cut-off limit of 1.0 indicating severe disability whereas 10/38 (26%) patients were affected to some extent with a score of <1.3, which indicates detectable difficulties in handling daily routines and need of assistance. Five patients could not participate in AMPS for practical reasons, one had complete deafness, two were under cardiac monitoring and two had no experience of AMPS related activities.

Regarding the degree of anxiety, depressive mood, and sleep disturbances the questionnaires were used to screen for symptoms, indicating two patients with moderate to severe depression with anxiety, and these received anti-depressant medication after further review. An additional 2–4 patients indicated minor depression/anxiety requiring no further action, in total any mood disturbance was noted in 14%. Twenty-two percentage of the patients reported insomnia on a regular or frequent basis and 6.5%

Table 4
Cognitive test results.

Degree of cognitive decline/difficulties. $n=43$	1, none	2, very mild	3, mild	4, moderate	5, moderate to severe	6, severe	7, very severe
(a) GDS score, Self-reported Global Deterioration Scale							
# patients	19	8	12	3		1	
%	44.2	18.6	27.9	7.0		2.3	

$n=40$	18–15, normal	14–13, mild	≤12, severe
(b) FAB, Frontal Lobe Assessment Battery[a]			
# patients	25	5	10
%	62.5	12.5	25

$n=39$	≥22, normal	21–17, mildly affected	16–10, moderately affected	9–0, severely affected
(c) RBMT, Rivermead Behavioural Memory Test[b]				
# patients	8	18	11	2
%	20.5	46.2	28.2	5.1

$n=42$	Wakefullness	Orientation	Alertness	Comprehension[c]	Repetition[c]	Naming[c]	Visuospatial	Memory	Arithmetic	Logic[c]	Judgement[c]
(d) NCSE, Neurobehavioral Cognitive Status Examination											
# severe	0	1	0	2	1	1	1	6	1	2	0
% severe	0	2.3	0	5	2.5	2.5	2.5	14.3	2.3	4.8	0
# moderate	0	0	1	1	0	1	4	4	4	1	0
% moderate	0	0	2.3	2.3	0	2.5	9.5	9.5	9.5	2.3	0
Total deviations % (mild to severe)	4.65	32.6	13.9	23.2	9.3		20.9	62.8	16.2	23.2	2.3

[a] Missing patients were due to non-Swedish native tongue (2) and complete deafness (1).
[b] Missing patients were because of non-Swedish native tongue (3) and complete deafness (1).
[c] Data are missing from three patients due to non-Swedish native tongue. It is to note that one patient scored severe disability in three domains, whereas all other 11 patients had unique scores of this magnitude. One patient could not participate at all due to complete deafness.

had excessive daytime sleepiness, one of whom when driving a car. Inadequate sleep quality was present in 10%.

Using the EQ-VAS, 25% reported 90–100% level of health status; 30.5% 80–89%; 16.7% 70–79%; and 25% scored below 70%, with two patients <20%. The mean value was 75.3% (95% CI ±18.8).

4. Discussion

This study shows that mild cognitive impairment is common in hypothermia-treated CA survivors. Despite mild impairment, survivors have a high level of functioning as reflected in the CPC categories, and their quality of life is good. Overt neurological findings are uncommon in a clinical examination. Clearly the outcome following TH-treated CA is dichotomized into survival with good neurological outcome or death.

We found CPC1 in 79% of survivors at 7.2 months which is comparable with Graves et al.[24] that found CPC1 at discharge in 53% and at 12 months in 73% in a large group of patients ($n=3754$ over a period of 13 years) treated with conventional methods after CA. Following TH CPC1 has been reported in 70% at 3 months[8] and in 97% at 6 months.[25]

We treated patients with hypothermia irrespective of initial cardiac rhythm and found only two patients with a severe neurological handicap (CPC 3) and no patient in a vegetative state. Recently published registry data confirms that severe sequels are uncommon 6–12 months following TH-treated CA with only 4% of patients in CPC 3–4 and 3/940 patients in vegetative state.[26] Although circumstances surrounding the CPR cannot be used to predict prognosis of individual patients[27] they have an impact on a group level. Accordingly, the difference in outcome between hospital 1 and hospitals 2 and 3 might be explained by differences in time to ROSC and initial rhythm. It is important to note that nine patients with another initial rhythm than VT/VF had good outcome justifying our inclusion to TH beyond the VT/VF-criteria.

The assessment protocol was chosen to detect a wide range of possible neurological deficits after CA. Care was taken to ensure that comparison with other outcome studies was possible, yet adding more detailed neurological descriptions of any sequelae. The tests have been used extensively in various disorders and conditions and are all sensitive, validated, and possible to perform within a limited time frame and without any particular equipment. The tests can be performed in an outpatient setting by a trained OT and an experienced physician.

The patterns of neurological defects were similar to that of published studies in CA-patients.[8,28] Although a direct comparative group analysis is not possible, there are several published studies employing identical tests.

The NCSE is a screening instrument for cognitive disabilities and the profile created can be used to distinguish between focal and more generalized disorders of higher cortical function.[12] Cut-off levels have been age-adjusted.[29] The most striking finding was memory disturbance which we found to some degree in a majority of patients (62%). This finding was confirmed in the RBMT, where 33% had moderate or severe difficulties and a further 46% had mildly affected long-term memory. This could represent the well known selective vulnerability of the hippocampus to global ischemia.[30] For comparison, O'Reilly et al.[31] found some degree of memory disturbance in 74% of survivors of in-hospital cardiac arrest without hypothermia treatment.

NCSE, like the Mini Mental Status Examination, may not be a very sensitive test to detect frontal lobe dysfunction in patients with preserved intellectual capacity. That a behavioral frontal lobe syndrome might be a part in severe cognitive dysfunction following prolonged cardiac arrest has previously been shown.[32] Interestingly, we found that 50% of our patients had signs of frontal lobe dysfunction at the FAB, a finding that might explain some of the subtle change in personality often reported by relatives to cardiac arrest survivors. It might also explain the processing difficulties in the AMPS test that we found in 26% of patients and that could not be explained by motor impairment.

Although experimental and clinical experience supports a direct relationship between the global anoxic injury of a cardiac arrest and the cognitive difficulties that we found[33] it has to be kept in mind

that cognitive dysfunction is common among survivors of critical illness other than CA.[34,35]

We found significant mood disturbance in 14% of patients which is lower than what has been found in cardiac arrest patients previously[36] and only slightly higher than what has been found in a control population (10%[37]). The level of sleep disturbance was comparable with that found in a healthy elderly population.[38]

The EQ-5D VAS scale is a measure of self-rated overall health status. We found a mean value of 75.3 in our material with a mean age of 62.4 years. In the population, the EQ-5D VAS level tends to decrease with increasing age and our value is lower than the mean of 79.8 found in a healthy cohort, 60–69 years old but identical to what was found in the 70–79 years age group[39] and similar to what has previously been found in cardiac arrest survivors.[40]

In summary, despite a preserved CPC, we found mild cognitive impairment in a majority of patients and similar to what has been found in patients not treated with TH. The NCSE and FAB tests were most informative, particularly when combined. These tests can easily be used as a screening procedure by an OT at 3–6 months following cardiac arrests. When disability is mild, patients and relatives can be given information about compensatory strategies and the benignity of the condition to avoid their worry for dementia. When disability is more severe, further testing and referral to a neurologist is warranted.

5. Conclusions

Mild cognitive impairment is common following hypothermia-treated cardiac arrest but has only minor effect on functional activity and quality of life. It is characterized by memory and executive, frontal lobe disturbance which could easily be detected by simple tests in an outpatient setting.

Conflicts of interest

None.

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References

1. Edgren E, Hedstrand U, Kelsey S, Sutton-Tyrrell K, Safar P. Assessment of neurological prognosis in comatose survivors of cardiac arrest. BRCT I Study Group. Lancet 1994;343:1055–9.
2. Herlitz J, Bang A, Gunnarsson J, et al. Factors associated with survival to hospital discharge among patients hospitalised alive after out of hospital cardiac arrest: change in outcome over 20 years in the community of Göteborg, Sweden. Heart 2003;89:25–30.
3. Jørgensen EO, Holm S. The natural course of neurological recovery following cardiopulmonary resuscitation. Resuscitation 1998;36:111–22.
4. Harukuni I, Bhardwaj A. Mechanisms of brain injury after global cerebral ischemia. Neurol Clin 2006;24:1–21.
5. Fukuda S, Warner DS. Cerebral protection. Br J Anaesth 2007;99:10–7.
6. The HACA Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346:549–56.
7. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346:557–63.
8. Tiainen M, Poutiainen E, Kovala T, Takkunen O, Happola O, Roine RO. Cognitive and neurophysiological outcome of cardiac arrest survivors treated with therapeutic hypothermia. Stroke 2007;38:2303–8.
9. 2005 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. Part 4: Advanced life support. Resuscitation 2005;67:213–47.
10. Bernard S, Buist M, Monteiro O, Smith K. Induced hypothermia using large volume, ice-cold intravenous fluid in comatose survivors of out-of-hospital cardiac arrest: a preliminary report. Resuscitation 2003;56:9–13.
11. Rundgren M, Rosen I, Friberg H. Amplitude-integrated EEG (aEEG) predicts outcome after cardiac arrest and induced hypothermia. Intens Care Med 2006;32:836–42.
12. Kiernan RJ, Mueller J, Langston JW, Van Dyke C. The Neurobehavioral Cognitive Status Examination: a brief but quantitative approach to cognitive assessment. Ann Intern Med 1987;107:481–5.
13. Fisher A. AMPS: Assessment of Motor and Processing Skills. Vol.1: Development, standardization and administration manual. 5th ed. Ft. Collins, CO: Three Star Press; 2003.
14. Kizony R. Relationships between cognitive abilities and the process scale and skills of the assessment of motor and process skills (AMPS) in patients with stroke. Occup Participation Health 2002;22:82–92.
15. Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a Frontal Assessment Battery at bedside. Neurology 2000;55:1621–6.
16. Makatura TJ, Lam CS, Leahy BJ, Castillo MT, Kalpakjian CZ. Standardized memory tests and the appraisal of everyday memory. Brain Injury 1999;13:355–67.
17. Lincoln NB, Tinson DJ. The relation between subjective and objective memory impairment after stroke. Br J Clin Psychol 1989;28 (Pt 1):61–5.
18. Buysse DJ, Reynolds 3rd CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193–213.
19. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–70.
20. Svanborg P, Åsberg M. A comparison between the Beck Depression Inventory (BDI) and the self-rating version of the Montgomery Åsberg Depression Rating Scale (MADRS). J Affect Disord 2001;64:203–16.
21. Reisberg B, Ferris SH, de Leon MJ, Crook T. Global Deterioration Scale (GDS). Psychopharmacol Bull 1988;24:661–3.
22. The EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199–208.
23. Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet 1975;1:480–4.
24. Graves JR, Herlitz J, Bang A, et al. Survivors of out of hospital cardiac arrest: their prognosis, longevity and functional status. Resuscitation 1997;35:117–21.
25. Bro-Jeppesen J, Kjaergaard J, Horsted TI, et al. The impact of therapeutic hypothermia on neurological function and quality of life after cardiac arrest. Resuscitation 2009;80:171–6.
26. Friberg H, Nielsen N. Hypothermia after cardiac arrest: lessons learned from national registries. J Neurotrauma 2009;26:365–9.
27. Wijdicks EF, Hijdra A, Young GB, Bassetti CL, Wiebe S. Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation. Neurology 2006;67:203–10.
28. Madl C, Holzer M. Brain function after resuscitation from cardiac arrest. Curr Opin Crit Care 2004;10:213–7.
29. Macaulay C, Battista M, Lebby PC, Mueller J. Geriatric performance on the Neurobehavioral Cognitive Status Examination (Cognistat). What is normal? Arch Clin Neuropsychol 2003;18:463–71.
30. Petito CK, Feldmann E, Pulsinelli WA, Plum F. Delayed hippocampal damage in humans following cardiorespiratory arrest. Neurology 1987;37:1281–6.
31. O'Reilly SM, Grubb NR, O'Carroll RE. In-hospital cardiac arrest leads to chronic memory impairment. Resuscitation 2003;58:73–9.
32. Peskine A, Picq C, Pradat-Diehl P. Cerebral anoxia and disability. Brain Injury 2004;18:1243–54.
33. Kadar T, Dachir S, Shukitt-Hale B, Levy A. Sub-regional hippocampal vulnerability in various animal models leading to cognitive dysfunction. J Neural Transm 1998;105:987–1004.
34. Griffiths RD, Jones C. Seven lessons from 20 years of follow-up of intensive care unit survivors. Curr Opin Crit Care 2007;13:508–13.
35. Sukantarat KT, Burgess PW, Williamson RC, Brett SJ. Prolonged cognitive dysfunction in survivors of critical illness. Anaesthesia 2005;60:847–53.
36. Grubb NR, O'Carroll R, Cobbe SM, Sirel J, Fox KA. Chronic memory impairment after cardiac arrest outside hospital. BMJ 1996;313:143–6.
37. Herrmann C. International experiences with the Hospital Anxiety and Depression Scale—a review of validation data and clinical results. J Psychosom Res 1997;42:17–41.
38. Vitiello MV, Larsen LH, Moe KE. Age-related sleep change: Gender and estrogen effects on the subjective–objective sleep quality relationships of healthy, noncomplaining older men and women. J Psychosom Res 2004;56:503–10.
39. Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. BMJ 1998;316:736–41.
40. Granja C, Cabral G, Pinto AT, Costa-Pereira A. Quality of life 6-months after cardiac arrest. Resuscitation 2002;55:37–44.