Review paper

Prediction of cognitive dysfunction after resuscitation – a systematic review

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Adv Interv Cardiol 2018; 14, 3 (53): 225–232
DOI: https://doi.org/10.5114/aic.2018.78324

A b s t r a c t

Cardiac arrest (CA) due to cardiovascular disease is the leading cause of death in developed countries. It is estimated that over 350,000 people in Europe suffer from out-of-hospital cardiac arrest. According to the literature, the longer the episode of cardiac arrest, the greater the risk of cognitive impairment, especially short-term memory, as well as immediate and delayed recall. Other common dysfunctions include attention deficits and executive function disorders. The aim of this systematic review was to summarize current research on cognitive impairment in patients after sudden cardiac arrest. The electronic databases PubMed/MEDLINE, OVID, Web of Science, and EBSCO were searched using the following key words: 'sudden cardiac arrest', 'out-of-hospital cardiac arrest', 'cognitive function', 'cognitive impairment', 'functional outcome', 'cardiopulmonary resuscitation'. The most recent studies from the last 7 years (2011–2018) were included. Cognitive disorders occurred in a broad range of cases: from 13% to even 100%. In one study, cognitive deficits did not occur at all. Amongst the reviewed articles only two studies were carried out on a large group of patients. The remaining studies were conducted on a small group of respondents; therefore there was no possibility to generalize the results to the entire population. The areas in which the most cognitive impairment occurred were memory, executive functions and visual–motor skills. One of the conclusions derived from the reviewed literature is the importance of continuous training of cognitive functions, especially for people with cardiovascular risk.

Key words: sudden cardiac arrest, resuscitation, out-of-hospital cardiac arrest, cognitive impairment, neuropsychological testing, in-hospital cardiac arrest.

Introduction

Cardiac arrest (CA) due to cardiovascular disease is the leading cause of death in developed countries [1]. Most cases of CA occur at home, which results in a high level of mortality [2]. It is estimated that over 350,000 people in Europe suffer from out-of-hospital cardiac arrest (OHCA) [3], approximately 186,000 are hospitalized because of CA, more than half of these people die within a year, and about 25,000–40,000 have cognitive impairment [4, 5]. Despite the improvement of resuscitation techniques and post-resuscitation care, the proportion of outcomes remains constant [6]. Cerebral ischemia and hypoxia associated with cardiac arrest cause a number of adverse biomechanical effects. The interruption of the blood supply to the brain (hippocampus, neocortex, medial temporal lobe) that occurs during CA can cause cognitive decline [5, 7–10]. The severity of symptoms depends on the extent of the brain damage, which is directly proportional to the duration of CA [11]. According to the literature, the longer the episode of CA, the greater the risk of cognitive impairment, especially short-term memory, as well as immediate and delayed recall. Other common dysfunctions include attention deficits and executive function disorders [12]. The neurological and cognitive status is the most important factor affecting the overall quality of life. Patients with prompt resuscitation who respond to stimuli after return of spontaneous circulation (ROSC) or follow instructions within 6–12 h after CA have a high probability of full recovery or only minor impairment of cognitive function. Amongst patients in a coma lasting 1–7 days, the occurrence and prevalence of cognitive impairment is uncertain, while a coma lasting more than 7 days after ROSC is associated with a bad neurological prognosis [3, 13].

Methods

The systematic review was carried out in accordance with the latest standards of systematic reviews published by the Institute of Medicine.

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Received: 21.03.2018, **accepted:** 17.06.2018.

Search strategy

The electronic databases PubMed/MEDLINE, OVID, Web of Science, and EBSCO were searched using the following key words: 'sudden cardiac arrest', 'out-of-hospital cardiac arrest', 'cognitive function', 'cognitive impairment', 'cognition', 'functional outcome', 'cardiopulmonary resuscitation' and 'neuropsychological tests'. The most recent studies from the last 7 years (2011–2018) were included. The search was limited to human studies that were published in English or in Polish languages. Individual keywords or their combinations were typed during the search, using the AND, OR operators, or both. The number of publications obtained in each search was filtered taking into account the inclusion criteria, i.e. patients after sudden cardiac arrest who have undergone cognitive assessment, which allowed a core/primary database to be created for the study. In the next step the abstracts and summaries were arbitrarily limited to selected articles. Finally, references and bibliographies of those articles were analyzed to broaden the original searches and the final list of references was created based on the relevance of the topic discussed.

Study selection

The review included studies on cognitive functioning after CA in adults. The following articles were excluded:
– articles published in languages other than English and Polish;
– studies with subsequent cognitive status testing repeated within 1 month;
– research on patients with brain damage;
– studies describing the same or overlapping patient sample; in this case, we used the latest article, which described both new data and data previously reported;
– studies with missing data which were crucial for the review.

The studies' eligibility was assessed on the basis of the title, summary and, if necessary, the full text, by two reviewers using the aforementioned selection criteria.

Data extraction

Both reviewers independently evaluated selected articles using a standardized data collection form (Table I) [5, 11, 12, 14–19]. Characteristics were as follows: first author, year of publication, study design, population, number of participants, average age at the beginning of the study, duration of resuscitation, time interval after CA followed by cognitive tests, in which there was a cognitive impairment, the result of cognitive impairment and the proportion of patients with cognitive impairment. The quality of the study was evaluated based on four criteria:
1) the availability of cognitive performance data at the beginning of the study;
2) the use of neuropsychological tests to assess cognition (Table II) [20–48];
3) description of inclusion and exclusion criteria;
4) the impact of factors that could interfere with the cognitive outcome, such as age and sex.

These qualitative criteria were chosen because they are widely used (criteria 3 and 4) and are specific to the study evaluating neurocognitive outcome (criteria 1 and 2).

Results and discussion

The results published by different authors vary significantly. Cognitive disorders occurred in a broad range of cases: from 13% (Lilja *et al.*) to even 100% (Alexander *et al.*) [14, 19]. In one study, cognitive deficits did not occur at all (Raina *et al.*) [15]. Such a significant difference could have been influenced by the quality and quantity of tests used to assess cognitive functions. Alexander *et al.* used a significant number of tests, which had an impact on the high level of detection of cognitive impairment [19]. In contrast, Raina *et al.*, who did not observe any cognitive impairment, used Mini-Mental State Examination (MMSE) and Telephone Interview Cognitive Status (TICS) to assess cognitive functions [15]. Nevertheless the use of MMSE does not guarantee accurate results [49]. In an earlier study Cronberg *et al.* drew attention to the fact that tests such as MMSE may be insufficiently sensitive for patients with preserved intellectual capacity [50].

Amongst the reviewed articles only two studies were carried out on a large group of patients (287 Lilja *et al.*, 249 Beesems *et al.*) [17]. The remaining studies were conducted on a small group of respondents [14, 29, 30, 41], so there was no possibility to generalize the results to the entire population. Some authors compared the results of OHCA patients to healthy controls matched for age, sex (Beesems *et al.*, Tiainen *et al.*) as well as education (Jaszke-Psonka *et al.*) [12]. The control group should not be composed of healthy people because it can lead to impairment exaggeration. Instead, it should rather include controls matched for risk factors, not age or gender only [19]. Buanes *et al.* used norms for healthy populations of other countries due to the lack of Norwegian standards. Raina *et al.* did not compare the obtained results to any control group. Lilja *et al.* compared their results to STEMI controls treated with percutaneous coronary intervention (matched for age, gender, country and time-point of hospitalization), whereas Alexander *et al.* [14, 19]. chose controls with acute coronary syndrome matched for age, gender, education, risk factors, previous cardiac events and the use of psychoactive medication.

The areas in which the most cognitive impairment occurred were memory [5, 11, 12, 14, 16, 19], executive functions and visual–motor skills [11, 12, 14, 16, 19], which is consistent with earlier studies: Lim *et al.* reported that the most common pattern of impairment in their patients was a combination of memory and motor deficits with variable executive impairment [51]; Sauve *et al.* found in their study that 72% of those subjected to

Table I. Cognitive status after sudden cardiac arrest

First author	Year of study	Design	Population	Baseline cognitive	*N*	Age (average)	Time of CPR/ time to ROSC	Therapeutic hypothermia	Follow-up duration [months]	Cognitive outcome measures[a,b]	Location of CA	Definition of cognitive impairment	Proportion of patients with cognitive impairment
Lilja [14]	2017	Follow-up study	Presumed cardiac origin	No	287	63 (33°C) 60 (36°C)	Time to ROSC [min] 20 (33°C) 21 (36°C)	Yes (148/287)	Approx. 6	RBMT FAB SDMT	OHCA	< 22 points < 14 points *Z*-score < 1	19 (13%) 33°C 21 (15%) 36°C
Jaszke-Psonka [12]	2016	Prosp. cohort	Coronary disease	No	30	52.9 ±8.8	No data	No data	3	BVMT BVRT (C/A)/S	No data	$p = 0.17$ $p < 0.001$	16 (53.3%) 12 (40.0%)
Raina [15]	2015	Observational study	Non-traumatic cardiac arrest (VF/VT, PEA, asystole)	No	29	60.8 ±16.3	No data	Yes (13/29)	1, 6, 12	ALFI–MMSE TICS	OHCA or IHCA	–	0
Buanes [5]	2015	Cohort	Coronary disease	No	30	62	No exact data	Yes (7/30)	42	PAL DMS	OHCA or IHCA	$p < 0.05$	8 (29%)
Tiainen [16]	2015	Randomized controlled trial	Acute myocardial infarction, arrhythmia	No	41	59	BLS: 8 (2–14) min ACLS: 14.5 (6–100) min Time to ROSC: 17 (7–33) min	Yes (all)	6	WAIS-R WMS WMS-R	OHCA	$p = 0.323$	21 (51%)
Beesems [17]	2014	Follow-up study	OHCA of unknown origin	No	249	63 ±12.6	No data	Yes (in all unconscious, except 3)	6–13	TICS	OHCA	$p < 0.001$	178/211 (84%)[c]
Orbo [18]	2014	Prospective study	OHCA of cardiac origin	No	45	60.4	Time to ROSC: 17.6 (1–60) min	Yes (19 – 42.2%)	3	VLT GPB WMS D – K RFT	OHCA	$p \leq 0.05$ (≤ –1.5 SD)	20 (44%)
Polanowska [11]	2014	Prospective study	Non-traumatic, normothermic cardiac arrest	No	14	58.4 ±10.3 years	No data	No	3, 6, 12	TMTA and B RAVLT BVRT DSFT WCST RCFT	OHCA	$p = 0.001$	8 (57.2%)
Alexander [19]	2011	Prospective study	Ventricular fib. (86%; rest – unknown)	No	30	56.5	Time to ROSC under 15 min in 19 patients; no data on BLS/ACLS	No	3	RAVLT BVMT-R TMTA and B WCST VFT BNT PPV GPB JLO VDT FTT	OHCA	$0.001 < p < 0.033$	In 10 (33%) mild impairment, in 20 (67%) severe impairment

[a]Tests in which dysfunction occurred. [b]For abbreviation and test description see Table II. [c]Not every patient enrolled in the study completed TICS. [d]Testing 3 ±1 days after the incident (only 21 patients cooperated to some extent and could be tested).

Table II. Cognitive assessment tools

Test	Abbreviation	Characteristics
Rivermead Behavioral Memory Test	RBMT	Memory test composed of 12 different memory tasks (assessing aspects of visual and verbal memory, recall, recognition, immediate and delayed memory) [20]
Frontal Assessment Battery	FAB	Developed to assess frontal lobe functions at bedside. Six tasks explore cognitive and behavioral domains that are thought to be under the control of the frontal lobes, most notably conceptualization and abstract reasoning, lexical verbal fluency and mental flexibility, motor programming and executive control of action, self-regulation and resistance to interference, inhibitory control, and environmental autonomy [21, 22]
Symbol Digit Modalities Test	SDMT	The subject is presented with a page headed by a key that pairs the single digits 1–9 with nine symbols. Rows below contain only symbols. The subject's task is to write or orally report the correct number in the spaces below. After completing the first 10 items with guidance, the subject is timed to determine how many responses can be made in 90 s [23]
Bender Visual-Motor Gestalt Test	BVMT	Assesses visual-motor functioning, developmental disorders, and neurological impairments. The test consists of nine index cards picturing different geometric designs. The cards are presented individually and test subjects are asked to redraw each one from memory before the next card is shown. Test results are scored based on the accuracy and organization of the reproductions [24]
Benton Visual Retention Test	BVRT	Measures visual perception and visual memory. The individual examined is shown 10 designs, one at a time, and asked to reproduce each one as exactly as possible on plain paper from memory. The test is untimed, and the results are professionally scored by form, shape, pattern, and arrangement on the paper [25]
Adult Lifestyles and Function Interview – Mini Mental State Examination	ALFI-MMSE	A telephone version of the MMSE as part of the Adult Lifestyles and Function Interview. The ALFI project was designed with a primary goal of estimating the incidence of cognitive impairment. Topics explored in the test include demographics, family history, health status, physical, auditory and visual functioning, memory problems, behavioral changes, depressive symptoms, and alcohol use [26]
Telephone Interview for Cognitive Status	TICS	Telemedical tool used to assess patients who have suffered a stroke or other neurological conditions [27]. It contains 22 questions and is a standardized test to evaluate neuropsychological functioning, used when a personal evaluation of global cognitive function is impractical or inefficient, for example, in epidemiological studies of large populations or in patients who are unable to attend the clinical facility [28]
Paired Associates Learning Test	PAL	Assesses visual memory and new learning. It consists of multiple trials in which the participant learns the location of one or more visual patterns on the screen [29]
Delayed Matching to Sample	DMS	Assesses forced choice recognition memory for non-verbalisable patterns, testing both simultaneous matching and short-term visual memory. In this test there is a time delay between the presentation of the sample and the comparison stimuli. By varying the length of the delay we can gain insight into how long the subject can retain information in their working memory [30]
Wechsler Adult Intelligence Scale	WAIS	The WAIS IQ test is one of the most popular psychological tools used to measure various capabilities in individuals. It evaluates vocabulary, arithmetic, visual-spatial or emotional capabilities [31]
Wechsler Memory Scale	WMS	Designed to measure different memory functions in a patient. Assesses global cognitive functioning in patients with suspected memory deficits [32]
National Adult Reading Test	NART	Test commonly used in clinical settings for estimating premorbid intelligence levels of English-speaking patients with dementia in neuropsychological research and practice. Involves pronunciation of irregular words [33]
Rey's Auditory Verbal Learning Test	RAVLT	It involves learning a list of unrelated words, which should be repeated after a short and a long period of time (approx. 30 min) [25]
Brief Visuospatial Memory Test	BVMT	Measures visuospatial learning and memory abilities [34]
Trail Making Test A and B	TMTA, TMTB	It assesses the ability to focus attention on visual and spatial material and the ability to switch attention between different stimuli, which is considered to be an executive function [25]
Wisconsin Card Sorting Test	WCST	Assesses concept formation, abstract reasoning and the ability to shift cognitive strategies in response to changing environmental contingencies [35]

Table II. Cont.

Test	Abbreviation	Characteristics
Boston Naming Test	BNT	Used for the assessment of confrontation naming ability [36]. Subjects are shown drawings of common objects one at a time and asked to name them orally [37]
Verbal Fluency Test	VFT	Test in which participants are given 60 seconds to produce as many unique words as possible from a category (semantic or phonemic) [38]
Grooved Pegboard	GPB	Assesses upper extremity motor speed and visual–motor coordination. The participant is asked to match grooved pegs to the holes in a board. The test can be performed for only the dominant hand or both hands separately [39, 40]
Peabody Picture Vocabulary	PPV	Patients are asked to choose one of four pictures which best identifies a spoken word [41]
Finger Tapping Test	FTT	Evaluates muscle control and motor ability in the upper extremities [42]
Visual Discrimination Test	VDT	Assesses processing speed. It requires the patient to discriminate between two lines of markedly different lengths [43]
Judgment of Line Orientation Test	JLO	Assesses visuospatial ability (the patient is asked to match the angle and orientation of lines in space) [44]
Number Location Test	NLT	Assesses visuospatial abilities [45]
Delis-Kaplan Executive Functioning System	D-K	Employs nine individual subtests designed to provide a comprehensive evaluation of psychomotor speed and executive functioning [46]
Rey's Complex Figure Test	RCFT	Evaluates visuospatial ability and visual memory. The subject is given a stimulus card and then asked to draw the same figure (first the subject has to copy it, then draw it from memory and subsequently after 30 minutes delay) [47]
Digit Span Forward Test	DSFT	Assesses working memory (storage capacity). Subjects are asked to recall a sequence of numerical digits – with increasingly longer sequences in each trial [48]

cognitive tests after CA had worse memory scores (especially delayed recall) [52]. Cronberg *et al.* obtained similar results – the majority of patients (62%) showed memory impairment of varying severity [10], which may have been the result of the susceptibility of the hippocampus to ischemia. However, not only patients after CA are at risk of cognitive impairment – concordant results were obtained when conducting tests on a group of patients hospitalized in Intensive Care Units or undergoing surgical procedures [53, 54]. Some patients diagnosed with cognitive disorders after CA might have had them before the incident. Therefore, it can be concluded that CA does not lead to specific changes in cognitive functioning. Due to the sudden and unpredictable nature of out-of-hospital cardiac arrest, it is difficult to assess the level of cognitive functioning before the incident. Lilja *et al.* reported that only half of the presented executive dysfunctions could have been caused by CA, which was confirmed by the STEMI controls results (attention and mental speed were the most affected among CA patients, whereas results for executive functioning and memory were comparable).

Cardiac arrest and the subsequent loss of blood flow through the brain tissue cause a number of biochemical changes resulting in brain damage. So far, several studies have shown that the use of therapeutic hypothermia (TH) after CA had a protective effect on brain tissue [55–57]. Therapeutic hypothermia is recommended for all patients with shockable cardiac rhythm who remain unconscious after ROSC [58]. Most of the studies included in the review did not show significant differences in cognitive function between TH patients and those who did not receive TH [14, 16, 17]. However, Alexander *et al.* concluded that their results may indicate effectiveness of therapeutic hypothermia, because TH patients had a lower level of cognitive impairment. Orbo *et al.* concluded that TH was a stronger predictor compared with coma duration for performance on the executive function tests – hypothermia treatment predicted better cognitive results. However, in a prior study Cronberg *et al.* indicated a high incidence of cognitive impairment in patients undergoing TH.

Knowing the influence of prolonged hypoxia on the central nervous system, it can be assumed that the shorter the period from cardiac arrest to ROSC or full consciousness is, the better the cognitive performance results will be. Orbo *et al.* and Jaszke-Psonka *et al.* did not confirm such a relationship. Weigl *et al.* studied individuals who experienced short CA during cardiac procedures and concluded that even a short episode of hypoxia could be the cause of cognitive decline [59]. However, Alexander *et al.* reported that patients who regained consciousness quickly (1–3 days) were more likely to present mild cognitive impairment (33%) in comparison to the patients who needed more time to recover (3–7 days) and were much more cognitively impaired (67%). This is in line with the previous studies: Sauve *et al.* suggested in their study that the persistency of cognitive disorders after CA may be estimated based on the duration of the unconsciousness period. Groswasser *et al.* noted better results of cognitive tests when the coma lasted less than 24 h from the occurrence of anoxic brain injury [60].

It can be hypothesised that the longer recovery after CA is, the better the cognitive functioning will be amongst the patients. Beesems *et al.* did not confirm this hypothesis, explaining it by the lack of daily challenges in hospital conditions, which would require the use of certain cognitive processes. In a small prospective study Lim *et al.* reported that impairments in memory and executive functioning remained the same, but there was a modest reduction in the number of patients with impairments in other domains (comparing outcomes at 3 and 12 months) [61]. Polanowska *et al.* reported that cognitive impairment occurred in all patients 3 days after the OHCA incident, whereas after 12 months the impairment was present in 57.2%. In this study an alarmingly large group of patients suffered from neurological disorders (including the vegetative state). After 12 months cognitive testing was performed on 14 patients, while 29 entered the study. Reviewers found this study to be of poor quality. Previously Hofgren *et al.* used cognitive tests and the Activities of Daily Living scale (ADLs) in CA survivors 2 years after the incident: recovery of cognitive functions to the expected level was not attained as only one person achieved a score equal to the cut-off results. It should be noted, however, that the level of cognitive functioning alone is not the most important element, because patients learn to cope with cognitive limitations over time and manage to live independently [15, 62]. Moderate cognitive impairment is not always connected with dependence or disability [16]. Apart from the cognitive status, several authors tested the level of independence (functional outcome) [15, 19] and the quality of life [15–17, 19]. For patients after CA independence in their environment and return to work are important, because it affects mood and the occurrence of depressive symptoms [15]. However, the occurrence of depression affects the results of cognitive tests [12], the process of rehabilitation [15] and the quality of life [63].

Conclusions and therapeutic implications

Cognitive impairment four years after CA seems to be comparable to early Alzheimer's dementia [5]. It seems that this mainly affects memory, with little effect on executive functions. Thus self-awareness of the occurrence of cognitive deficits is important because it allows new strategies to be developed for dealing with various challenges, including return to work.

One conclusion derived from reviewing the literature is the importance of continuous training of cognitive functions, especially for people with cardiovascular risk. In this group of patients, qualified neuropsychological care and rehabilitation focused on the training of cognitive functions should be provided. Future studies should provide information about selection of tests most suitable for cognitive impairment screening.

It is important to achieve a level of independence after CA that allows patients to return to work, which has a positive psychological effect. It was established that CA survivors may experience symptoms of depression for several months after the incident [15]. Therefore, caregivers for patients after CA should be able to assess the mood of the care recipients, because depression affects the rehabilitation process, and thus the level of independence [15, 45, 63].

Conflict of interest

The authors declare no conflict of interest.

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