

## Clinical paper

# Cognitive function and health-related quality of life four years after cardiac arrest<sup>☆</sup>



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## ABSTRACT

**Aim:** Neuropsychological testing has uncovered cognitive impairment in cardiac arrest survivors with good neurologic outcome according to the cerebral performance categories. We investigated cognitive function and health-related quality of life four years after cardiac arrest.

**Methods:** Thirty cardiac arrest survivors over the age of 18 in cerebral performance category 1 or 2 on hospital discharge completed the EQ-5D-5L and HADS questionnaires prior to cognitive testing using the Cambridge Neuropsychological Test Automated Battery. The results were compared with population norms.

**Results:** Twenty-nine per cent of patients were cognitively impaired. The pattern of cognitive impairment reflects dysfunction in the medial temporal lobe, with impaired short-time memory and executive function slightly but distinctly affected. There was a significant reduction in quality of life on the EQ-VAS, but not on the EQ index.

**Conclusion:** Cognitive impairment four years after cardiac arrest affected more than one quarter of the patients. Short-term memory was predominantly affected.

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## 1. Introduction<sup>1</sup>

Cognitive function in cardiac arrest (CA) survivors is reported to be favourable in the majority of patients.<sup>1–3</sup> The most frequently used cognitive outcome has been the cerebral performance categories (CPC) upon discharge, as specified in the Utstein template.<sup>4,5</sup>

After its introduction in 1975, the CPC became an important tool for improving the assessment of outcomes after severe brain damage. In recent decades, it has become increasingly evident that the CPC is too crude to assess more subtle changes in cognitive function that may appear after CA. Neuropsychological testing has uncovered cognitive impairment in CA survivors with good cerebral outcome according to the CPC.<sup>6–8</sup> The use of CPC as a robust cerebral outcome measure has therefore been questioned.<sup>9</sup>

With regard to diagnostic accuracy, traditional neuropsychological testing provides a detailed assessment of cerebral function. The drawback is that the method is time-consuming and requires highly specialised personnel. The ideal diagnostic tool for clinical use must provide a sufficiently detailed assessment of cognitive function and be easy to administer. We have previously used the Cambridge Neuropsychological Test Automated Battery (CANTAB) on a CA population treated with therapeutic hypothermia.<sup>10</sup> The method is suited to clinical work and comparison across different cultures and languages.<sup>11</sup> In this study, we test the hypothesis that

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<sup>1</sup> List of uncommon abbreviations: HADS, Hospital Anxiety and Depression rating Scale; CANTAB, Cambridge Neuropsychological Test Automated Battery; MOT, Motor Screening (test in CANTAB); PAL, Paired Associates Learning (test in CANTAB); DMS, Delayed Matching to Sample (test in CANTAB); SOC, Stockings of Cambridge (test in CANTAB); IED, intra-/extradimensional set shift (test in CANTAB).

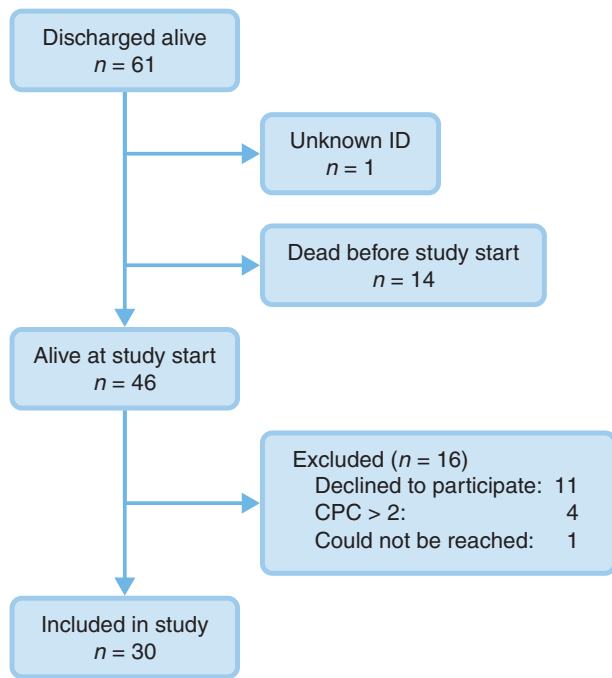


Fig. 1. Flow chart showing included and excluded patients.

cognitive impairment persists in long-term CA survivors with good cerebral outcome according to the CPC compared with an age and gender-matched population norm. Our secondary objectives were to investigate health-related quality of life and whether primary shockable rhythm, the location of CA, therapeutic hypothermia or length of stay in the intensive care unit (ICU) could predict long-term cognitive function after CA.

## 2. Methods

### 2.1. Patients

Subjects from a cohort of patients discharged alive after cardiac arrest in Bergen between 1 December 2008 and 30 November 2009, above the age of 18 and alive in October 2012, were considered for inclusion. Data from this patient cohort have previously been published.<sup>12</sup> Patients with a CPC above 2 on hospital discharge and patients who could not be reached or had an unknown identity were excluded (Fig. 1). The patients included were tested at a single time point a median of 3.6 years (ICR: 3.4–3.8) after CA.

### 2.2. Test setting

The Hospital Anxiety and Depression rating Scale (HADS) (Ageing and health, Oslo University Hospital, Ullevål, Bygn. 37, 0407 Oslo, Norway) and the EQ-5D-5L (EuroQol Group, Marten Meesweg 107, 3068 AV Rotterdam, the Netherlands) were sent by post to all eligible patients, along with written information about the study, a consent form and a pre-paid return envelope. Participants who returned the initial forms were contacted by telephone to schedule cognitive testing. Participants who did not return the forms were contacted by telephone for consent. If consent was given, they were reminded to return the forms and cognitive testing was scheduled. CANTAB (Cambridge Cognition, Tunbridge Court, Tunbridge Lane, Bottisham, Cambridge CB25 9TU) test sessions took place at Haukeland University Hospital and lasted approximately one hour. For participants unable to travel to the hospital, testing was arranged at a health facility nearer where they lived.

### 2.3. Test methods

EQ-5D-5L was used to evaluate health-related quality of life. EQ-5D-5L is a self-administered questionnaire assessing five dimensions of health. It has five levels for each dimension and an overall self-estimate of health on a visual analogue scale (EQ-VAS). The five dimensions are mobility, self-care, usual activities, pain/discomfort and anxiety/depression. We report EQ-VAS and health index (EQ-index) calculated on the basis of values for the five dimensions.<sup>13</sup>

HADS was used to screen for anxiety and depression. It is a self-administered questionnaire that yields separate scores for depression and anxiety.<sup>14</sup> A score  $\geq 8$  indicates anxiety or depression.<sup>15</sup>

Cognitive function was measured using CANTAB,<sup>11</sup> a touch-screen, computer-based cognitive function assessment tool featuring a total of 22 tests for several cognitive domains. Language proficiency is only needed for the verbal instructions prior to each test, since all task stimuli are non-verbal, consisting of geometric designs or simple shapes. We assembled a battery of five tests to assess memory and executive functions. Assistants can administer the test battery in 50–70 min and the results are immediately available. Several outcome measures are available for each test, reported either as a raw score or z-score. The z-score is the number of standard deviations the patient's score differs from an age and gender-matched British population mean. For the classification of cognitive impairment (CI), we report z-scores from ten parameters based on test-retest reliability.<sup>16</sup> Five of the ten parameters represent memory and five represent executive function. Cognitive impairment was defined as having two out of ten z-scores below  $-2.0$ , or three out of ten z-scores below  $-1.5$ .<sup>17</sup> The test battery consisted of the following tests:

#### 2.3.1. Motor Screening

A simple introduction to the test apparatus and screening for visual and motor impairment that may interfere with cognitive testing. The subject has to touch X-marks of different colours on the screen as they appear.

#### 2.3.2. Paired Associates Learning (PAL)

A test of visual episodic memory and learning. Six or eight boxes are displayed. All of them are opened in random order, and some contain a pattern. The patterns are then displayed one at a time, and the subject must touch the box where each pattern is hidden. The test becomes progressively more difficult in eight stages. If the subject makes an error, patterns in that stage are re-presented. The test terminates after ten trials in any given stage.

#### 2.3.3. Delayed Matching to Sample (DMS)

A test of delayed memory and forced decision-making. A non-figurative pattern is displayed on the screen. Subjects must recall it and distinguish it from three similar patterns after a delay of 0, 4 or 12 s.

#### 2.3.4. Stockings of Cambridge (SOC)

A test of executive function, specifically spatial planning and spatial working memory. The subject has to move coloured circles arranged in stacks to match a given template. Difficulty increases with the number of moves required. Should the subject make more than double the number of moves required for the simplest solution, the problem is terminated. If three problems in a row are terminated, the entire test is terminated.

#### 2.3.5. Intra-/extradimensional set shift (IED)

A test of executive function, attention and flexibility. The subject has to select the correct figure from two alternatives according

to a rule that is acquired from feedback (correct/incorrect). After six subsequent correct selections, the rule changes as the test progresses to the next stage. The subject must discover new rules and adhere to them in order to progress through up to nine stages. The stages include reversal, intradimensional shift and extradimensional shift. The test terminates after 50 trials in any given stage.

#### 2.4. Data handling

Data relating to CA and resuscitation were retrieved from the original cohort.<sup>12</sup> HADS and EQ-5D-5L questionnaires were scored and reviewed by EAB and KKS. Data about medical history and treatment following the return of spontaneous circulation (ROSC) were retrieved retrospectively from the electronic patient journal by EAB. All data were registered in a dedicated database in Helse Bergen by EAB and KKS.

#### 2.5. Statistics

Mean scores are reported with the 95% confidence interval in brackets. Categorical data were analysed using chi-square tests without continuity correction, and confidence intervals for the difference between proportions were calculated using the Agresti–Caffo method.<sup>18</sup> Correlations were calculated using Pearson's product-moment correlation. Simple and multiple regressions were performed to investigate whether cognitive function could be predicted. Survival data were retrieved from the electronic patient journal and compared to Norwegian life tables.<sup>19</sup> Life tables for 2009 were used for subsequent years, since mortality.org only contained life table series up to 2009. All statistical analyses were conducted in R version 3.1.1.<sup>20</sup>

#### 2.6. Ethics

The study was conducted in accordance with the protocol approved by the Regional Committee for Medical and Health Research Ethics (2012/1701/REK vest). Written consent was obtained from all subjects.

### 3. Results

#### 3.1. Demographic and medical characteristics

Of the initial 61 CA survivors, one had unknown identity. Forty-six of the remaining 60 were alive at the start of the study. Four had CPC > 2 on hospital discharge, one could not be reached and 11 declined to participate (Fig. 1). None of the 30 patients included had known pre-existing brain damage or brain disease, dementia, psychiatric disease or were using or abusing central inhibiting or stimulating medication. There were no statistically significant differences in the distribution of age, gender, medical history or treatment between included patients and patients who declined to participate or could not be reached (Table 1).

#### 3.2. Treatment

Of the 30 included patients, 24 had coronary angiography performed during their hospital stay, while 16 had percutaneous coronary intervention performed. Only 1 of 30 had surgery with coronary artery bypass grafting, while 7 of 30 were treated with therapeutic hypothermia (TH). The duration of resuscitation was longer among the included patients than among the patients who declined to participate or could not be reached (Table 1).

#### 3.3. Survival

At the start of the study, 14 of 55 Norwegian patients with CPC ≤ 2 discharged alive with known identity were deceased (Fig. W1). The expected number of deaths in an age and gender-matched Norwegian population was 5.0 (standardised mortality ratio: 2.8; 95% CI: 1.6–4.5;  $p < 0.001$ ).<sup>19</sup>

#### 3.4. Depression and health-related quality of life

The mean score for EQ-VAS was 70.6 (95% CI: 63.4–77.8), compared to 80.0 (95% CI: 79.1–80.9) for an age and gender-matched Danish normal population.<sup>21</sup> The mean score for the EQ-index was 0.85 (95% CI: 0.79–0.90), compared to 0.86 (95% CI: 0.85–0.87) for the same reference population. The mean score for HADS-A was 3.7 (95% CI: 2.6–4.9) and 3.5 for HADS-D (95% CI: 2.2–4.7). For HADS-A, 2 of 30 (7%) patients scored ≥ 8, suggesting anxiety, whereas for HADS-D, 5 of 30 (17%) patients scored ≥ 8, suggesting depression. Correlations between cognitive function and depression or health-related quality of life were moderate and not statistically significant (Table W1).

#### 3.5. Cognition

All participants passed the Motor Screening test and were allowed to attempt the cognitive tests. According to the criteria, 29% (8/28; 95% CI: 15–47%) of the patients were cognitively impaired.<sup>17</sup> One of them had CPC 2 on hospital discharge. Nine of the ten z-scores had mean values lower than zero, and three of them were statistically significant from zero (Table 2 and Fig. 2). Only one remained so after adjusting for multiple testing. All significant z-scores represent visual memory. To test sensitivity, we performed bootstrap tests and constructed bootstrap confidence intervals for the mean of the ten z-scores. The results (not shown) were very similar to the results of the *t*-tests, both for *p*-values and confidence intervals.

In the multiple regression analysis, OHCA was a statistically significant predictor, with OHCA indicating better cognitive function (Table 3).

For reversal stages (stages 5, 7 and 9) of the intra-/extradimensional set shift (IED), the mean number of errors was 18.7. For non-reversal stages (stages 4, 6 and 8), the mean number of errors was 16.1 (95% CI for difference: –1.4 to 6.5;  $p = 0.20$ ). The total number of trials in IED intradimensional shift (ID, stage 6) was 6.5 (95% CI: 5.3–7.7) versus 24.8 (95% CI: 18.0–31.6) for the extradimensional shift (ED, stage 8) (difference: 18.3; 95% CI for difference: 11.8–24.8;  $p < 0.001$ ) (Fig. 3).

For the Delayed Matching to Sample (DMS) percentage correct at 0 s delay, the mean was 81.4 (95% CI: 75.4–87.5), whereas, at 12 s delay, the mean was 68.2 (58.8–77.6) (difference: 13.2; 95% CI for difference: 5.7 to 20.8;  $p = 0.001$ ,  $n = 28$ ) (Fig. W2).

### 4. Discussion

The main finding in this study is that cognitive impairment persists in 29% (95% CI: 15–47%) of CA survivors with good neurological outcome at hospital discharge four years after arrest.<sup>10,22</sup> The pattern of impairment indicates dysfunction in medial temporal lobe structures, as seen, for instance, in early Alzheimer's dementia.<sup>23</sup> We found memory impairments in the Paired Associates Learning (PAL) and a marked decrease in correct answers at 12 s delay, compared to 0 s delay, in the Delayed Matching to Sample (DMS). Both findings correlate with the hippocampus being affected.<sup>24</sup> As DMS and PAL both have spatial properties, low scores in both tests indicate that the medial temporal lobes are affected. These structures are important for processing spatial information.

**Table 1**  
Demographic and medical characteristics.

	Included		Declined <sup>a</sup>		95% CI <sup>b</sup>	P-value
Age (mean)	62		61		-16 to 14	0.90
Male gender	24/30	80%	10/12	83%	-26 to 25	0.80
Medical history						
No previous illness	6/30	20%	4/12	33%	-43% to 15%	0.36
Coronary disease	12/30	40%	4/12	33%	-25% to 35%	0.69
Heart failure	8/30	27%	2/12	17%	-20% to 33%	0.49
Hypertension	12/30	40%	4/12	33%	-25% to 35%	0.69
Lung disease	5/30	17%	1/12	8%	-18% to 27%	0.49
Diabetes	5/30	17%	3/12	25%	-37% to 17%	0.53
Stroke	4/30	13%	0/12	0%	-10% to 27%	0.18
Malignancy	5/30	17%	0/12	0%	-7% to 31%	0.13
Smoke	9/29	31%	3/11	27%	-29% to 31%	0.82
Hypercholesterolemia	11/30	37%	4/12	33%	-28% to 32%	0.84
Primary rhythm						0.43
Ventricular fibrillation	23/29	79%	6/11	55%	-	-
Ventricular tachycardia	2/29	7%	1/11	9%	-	-
Pulseless electric activity	2/29	7%	2/11	18%	-	-
Asystole	2/29	7%	2/11	18%	-	-
Presumed cause of arrest						0.32
Cardiac	26/30	87%	8/12	67%	-	-
Respiratory	2/30	7%	2/12	17%	-	-
Drowning	0/30	0%	1/12	8%	-	-
Trauma	1/30	3%	0/12	0%	-	-
Other	1/30	3%	1/12	8%	-	-
Resuscitation						
Duration of resuscitation (s)	1086		282		-1297 to -310	0.002*
Pre-hospital cardiac arrest	17/30	57%	6/12	50%	-21% to 32%	0.69
Witnessed cardiac arrest	28/30	93%	10/12	83%	-12% to 36%	0.32
Bystander CPR	26/60	87%	6/12	50%	-63% to -5%	0.01*
Treatment						
Coronary angiography	24/30	80%	7/12	58%	-9% to 51%	0.15
PCI	16/30	53%	5/12	42%	-21% to 41%	0.49
CABG	1/30	3%	1/12	8%	-28% to 12%	0.49
Therapeutic hypothermia	7/30	23%	3/12	25%	-32% to 24%	0.91

CI, confidence interval; CPR, cardio-pulmonary resuscitation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

<sup>a</sup> Declined participation, unknown ID or no contact established.

<sup>b</sup> 95% CI of mean/percentage difference.

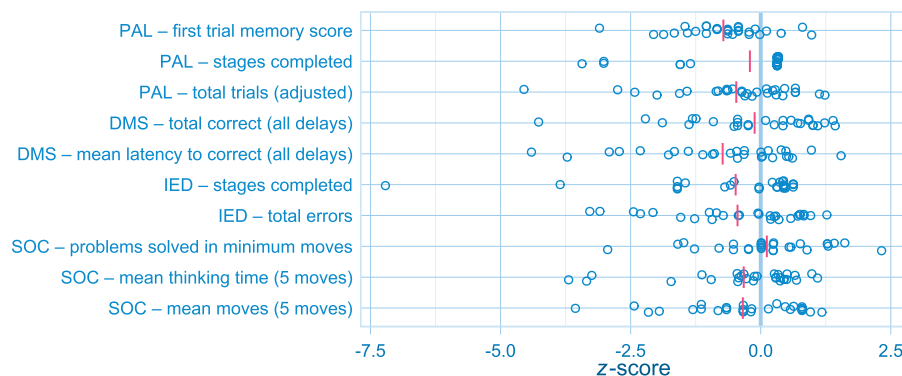
\* P-value < 0.05.

**Table 2**  
Mean z-score for ten outcome parameters from four CANTAB tests.

	n	Mean z-score	95% CI	P-value
PAL – first trial memory score	30	-0.72	-1.03 to -0.41	<0.001*
PAL – stages completed	30	-0.21	-0.63 to 0.22	0.33
PAL – total trials (adjusted)	30	-0.47	-0.93 to -0.01	0.05*
DMS – total correct (all delays)	28	-0.12	-0.62 to 0.39	0.64
DMS – mean latency to correct (all delays)	28	-0.73	-1.29 to -0.17	0.01*
SOC – problems solved in minimum moves	29	0.12	-1.14 to 0.17	0.56
SOC – mean thinking time (5 moves)	29	-0.33	-0.94 to 0.05	0.17
SOC – mean moves (5 moves)	29	-0.34	-0.30 to 0.53	0.12
IED – stages completed	28	-0.48	-0.80 to 0.14	0.14
IED – total errors	28	-0.45	-0.78 to 0.09	0.08

CI, confidence interval; PAL, paired associates learning; IED, intra-/extradimensional set shift; DMS, delayed matching to sample; SOC, stockings of Cambridge.

\* P-value < 0.05.



**Fig. 2.** Dot plot showing patient z-scores on 10 parameters from 4 CANTAB tests (n = 28, 29 or 30).

**Table 3**  
Regression of mean z-score on possible predictors.

	Multiple regression			Simple regression		
	Estimate <sup>a</sup>	P-value	95% CI	Estimate <sup>a</sup>	P-value	95% CI
Intercept	−0.56		−0.95 to −0.17			
Non-shockable rhythm	0.36	0.28	−0.32 to 1.04	0.35	0.25	−0.26 to 0.99
OHCA	0.52	0.04	0.04 to 1.00	0.37	0.08	−0.04 to 0.79
Therapeutic hypothermia	−0.20	0.63	−1.03 to 0.64	−0.08	0.74	−0.59 to 0.42
LOS ICU	−0.02	0.67	−0.10 to 0.07	−0.01	0.81	−0.06 to 0.05

$R^2 = 0.23$ . Adjusted  $R^2 = 0.09$ .

CI, confidence interval; OHCA, out-of-hospital cardiac arrest; LOS, length of stay; ICU, intensive care unit.

<sup>a</sup> Regression coefficient.

Several mechanisms for ischaemic brain damage have been identified. They include impaired cerebral reperfusion, apoptosis and alterations in gene expression, chemical phenotype and unfolded protein response.<sup>25,26</sup> In severe cases of ischaemic brain damage, the histopathologic pattern shows a typical distribution affecting the medial temporal lobes, cerebellum and neocortex.<sup>27</sup> These areas of the brain control memory and executive functions. Considering the physiologic substrate, one would expect the executive functions to be affected in our patients. This has previously been documented in CA survivors one and two years after an arrest.<sup>8,10</sup> The five selected z-scores representing executive functions were not affected in our patients. Hence, a detailed analysis of the intra-/extradimensional set shift (IED) test was performed in order to look for similarities between CA survivors, on the one hand, and patients with Alzheimer's dementia and patients with frontal variant frontotemporal dementia, on the other. These patients have lesions in regions of the brain that are also at risk in global

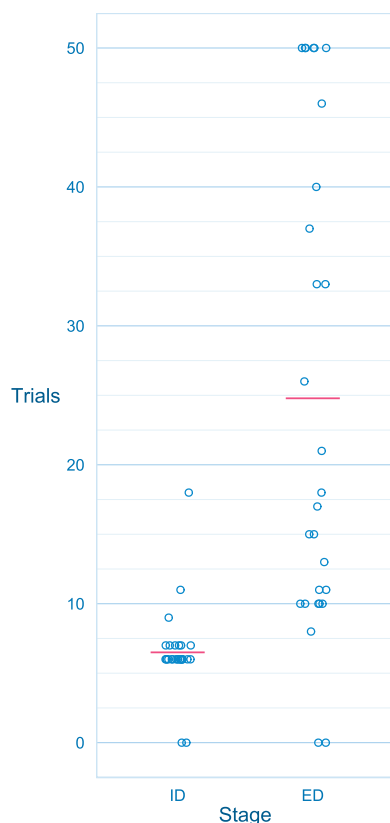
hypoxia. Patients with frontal variant frontotemporal dementia show decreased performance on reversal stages of the IED, which correlates with social disinhibition and inappropriate behaviour.<sup>28</sup> Such a finding might correspond to reports of personality changes and altered behaviour in CA survivors. Patients with Alzheimer's dementia show signs of excessive suppression of irrelevant information, a trait which corresponds to the number of trials in the Extradimensional Shift (ED) stage of the IED.<sup>23</sup> We found no pattern in the IED suggesting similarities with frontal variant frontotemporal dementia. There was, however, a pattern comparable to the one found in early stages of Alzheimer's dementia (Fig. 3). This may be explained by the 'creative hypothesis', whereby patients have many creative solutions to a problem at hand but fail to take previously irrelevant information into account.<sup>23</sup>

Increased mortality among CA survivors who were cognitively impaired might explain the low frequency of cognitive impairment in our material.<sup>29</sup> Our CA survivors have a standardised mortality rate of 2.8 (95% CI: 1.6–4.5), compared to an age and gender-matched Norwegian population. The mortality is higher than expected up until three years after CA (Fig. W1). If excess mortality were to explain the performance in cognitive tests, one would expect both memory and executive functions to be close to the norm. Memory impairment was clear in our patients, but executive functions were only slightly affected in the extradimensional shift stage of the IED. An alternative explanation is that patients have developed strategies to deal with executive dysfunction over the years following CA. This is not unlikely, since executive dysfunction may improve through a mindful approach to real-life tasks that pose problems.<sup>30</sup> In contrast, the treatment of amnesia is limited.

The quality of life report is similar to a Danish age and gender-matched reference population when measured on the EQ-index derived from the five dimensions of health, but significantly lower than the reference when measured on the EQ-VAS. We have no clear explanation for this difference. One could speculate that cerebral ischaemia reduces spatial awareness and thus affects patient responses to visual analogue scales. However, this would question the use of visual analogue scales in large patient groups, and there is no scientific basis in our study to support this.

In the regression analysis, OHCA appears to be a predictor of improved long-term CF. Due to the small sample size, multiple variables in the model and a p-value close to the limit of significance, we question the reproducibility of such a finding. Repeated studies with larger sample sizes are needed to establish causality.

The main strength of our study is standardised, detailed cognitive testing using computer-based test delivery. The two investigators followed a strict protocol and cognitive testing was conducted in public health facilities to ensure similar conditions for all patients. Limitations include the small sample size and lack of information about physical health at the time of investigation. A lack of Norwegian population norms has led us to use Danish norms for EQ5D and British norms for CANTAB, both of them close approximations of the parent population, in our opinion.



**Fig. 3.** Dot plot showing number of trials in the intradimensional set shift stage (ID) and the extradimensional set shift stage (ED) of the intra-/extradimensional set shift test (IED) ( $n = 28$ ).

Given a European population of 740 million and 3.7 million hospital beds, an estimated 186,000 persons are discharged following CA in Europe each year.<sup>31–34</sup> At least 90,000 of these patients are still alive one year after CA, and between 25,000 and 40,000 of them will have mild cognitive impairment.<sup>10,29,35</sup> The health impact is large in a European perspective and, in our opinion, it must be systematically addressed. Patients and their families need to be informed about the possibility of cognitive impairment following CA. If there is any suspicion of cognitive impairment that affects quality of life one year after CA, it should be documented. Thorough neuropsychological evaluation on such a scale is not feasible, since it is time-consuming and dependent on highly trained personnel. In our opinion, CANTAB can serve as a screening tool to identify patients for neuropsychological evaluation where cognitive impairment is suspected.

## 5. Conclusions

Cognitive impairment four years after cardiac arrest seems comparable to early Alzheimer's dementia. Memory appears to be predominantly affected, with executive functions being slightly affected.

## Conflicts of interest

The authors declare no conflicts of interest.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.resuscitation.2014.12.021>.

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